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ORIGINAL ARTICLES

PERIOSTEAL CHEST WALL PAIN AS PART OF THE POST-MYOCARDIAL-INFARCTION SYNDROME

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Within a few months, essentially identical observations were made on 2 patients with myocardial infarction who suffered from painful chest distress that was neither of anginal character, nor of neuromuscular origin, nor did it originate in the pleura or pericardium. It was of periosteal origin, presumably of an allergic-inflammatory etiology. It was promptly relieved by the local injection of a corticosteroid.

Case Reports. CASE 1. This 54-year-old priest had diverticulitis for 4 years, ultimately leading to a stenosis of the sigmoid colon. He was known to be normotensive and his effort capacity was good. On May 3, 1958, he had an ice cold drink, almost immediately developed chest pain that extended from the center to the right shoulder, he perspired profusely and the pain spread into both arms. He was hospitalized and an electrocardiogram showed evidence of an acute diaphragmatic myocardial infarction. He was discharged on June 11, 1958, and rested.

On June 15, there developed painful distress about the left scapular area and the pain persisted for hours. At midnight the patient was awakened by severe pain that extended from the midchest area to the right shoulder; there was no sweating; the pain persisted and on deep breathing it was aggravated over the right upper chest area. He was hospitalized on June 16. On examination the temperature was 99 3/5° F., the blood pressure 110/65; there was nothing remarkable over the lungs nor over the heart; there was pressure discomfort over the right third costochondral junction. An electrocardiographic study revealed evidence of the previous myocardial infarction, of diaphragmatic location with some involvement of the ventral and left lateral areas; there were no S-T deviations. The sedimentation rate was 36 mm. per hour and the leukocyte count was 10,300. Chest pain persisted, was aggravated by breathing, by changes in the position of the trunk, and by pressure over the second and third right costochondral junctions. An injection of 20 mg. of hydrocortisone was given subperiosteally into each of these two areas and the pain was promptly relieved. There developed occasional cough, and there were fine rales over both bases posteriorly. The heart rate was persistently elevated. There was no pericardial friction rub and no gallop rhythm. On June 17, a differential count showed 6% eosinophils and the same percentage was present on June 19, at which time the leukocyte count was 6,900. The transaminase test on June 18 was 89 units. On June 17, a roentgenographic study of the chest revealed a small area of density below the right hilus and adjacent to the right heart border, suggesting a small patch of pneumonitis; there also were horizontal, sharply demarcated densities on both the right and left sides a short distance above

the diaphragm and there was a minimal pleural reaction at the right base laterally situated in the region of the costophrenic sulcus. Other laboratory data were noncontributory. The temperature did not drop below 99° F. The only medication was 0.3 gm. of aminopyrin, t.i.d., that was started on June 17 to be given until June 22. In the early morning of June 20, the patient was awakened by severe chest pain necessitating morphine. There was pressure discomfort over the right fourth costochondral junction and over the medial end of the left costal arch. The patient described the pain as like a knife that was twisted inside of his chest, steady in character, extending from the center of the sternum to the left and right ribs, aggravated by deep breathing and any motion. There were a few fine rales over the left base posteriorly and over the right base laterally. A few hours later, 20 mg. of hydrocortisone was injected subperiosteally at the fourth right costochondral junction and at the left costal arch, respectively, and relief was obtained within a few hours. On that date, the temperature reached a maximum of 101° F. Severe chest pain recurred in the evening of June 20 and the morning of June 21, chiefly localized over the right anterior ribs and along the left costal arch and made worse by coughing. On June 21, 20 mg. of hydrocortisone was again injected into the left costal area and prompt relief was obtained. The temperature on this day rose to 100 4/5° F. On June 22, there was left precordial and left scapular pain aggravated by breathing. The temperature reached 100 3/5° F. An electrocardiographic study on June 22 showed, as compared with June 16, no changes in the limb Leads and $V_{5,6}$, but in Leads $V_{2,3}$ the S-T segments had risen slightly above the baseline and the voltage of T had somewhat increased resulting in a plus-minus shape in V_2 and positive in V_3. Starting on June 21, the patient received 0.6 gm. aspirin compound, 15 mg. Thorazine, and 32 mg. Darvon, each t.i.d. In the morning of June 23 the patient experienced severe left-sided chest pain and on examination there was a pleural friction rub that extended from the fourth and fifth rib parasternally to the anterior axillary line. The patient stated that it hurt to lie on the left side. On that day the temperature reached 101° F., the leukocyte count was 11,300 with 3% eosinophils and the transaminase test was 30 units. Bacteriologic study of the sputum revealed normal findings and the liver function was found to be normal. At no time could there be heard a pericardial friction rub.

Subsequently, the patient was completely free of distress, the temperature had reached a normal level by June 27 and the patient was discharged. He returned to work but on February 1, 1959, there was another attack of chest pain. Subsequently, chest pains occasionally recurred, lasting from a few hours to a couple of days. These were not related to exertion or excitement; they were aggravated by breathing; the character of the pain was sometimes sharp and shooting and sometimes dull and gnawing. An injection into the chest wall, given by the familiy physician who had received our previous reports, gave relief for quite a while. By the end of August, the patient developed abdominal pains, fever, and bowel movements were inadequate. There was tenderness in the left lower quadrant. In the electrocardiogram, the voltage of T had increased in Lead II and across the precordium. Further studies revealed a partial obstruction in the sigmoid area. An operation was performed with the findings of an inflammatory granulomatous tumor on the basis of diverticulitis, the sigmoid colon was resected, and the patient made an uneventful recovery. There were no further episodes of chest pains.

CASE 2. This patient, a housewife, was first studied at the age of 53. She fatigued easily and there was occasional pain over the upper anterior chest wall which could be readily brought on by pressure over the third, fourth, and fifth costochondral junctions. She did not suffer from angina pectoris. The findings with respect to the heart and blood pressure were normal. The serum cholesterol level was 455 mg. per 100 ml. and a number of subsequent studies revealed persistence of elevated figures. The electrocardiogram was abnormal in that the intrinsicoid deflection in several Leads measured 0.04 sec. and T was low and notched in Leads I, aV_L, $V_{4,5}$, and negative in $V_{1,2,3}$. A radioactive iodine take-up study done somewhat later revealed normal findings.

On June 25, 1958, effort angina started and this was followed by angina at rest. On June 28 the electrocardiogram revealed S-T depressions in Leads I, II, III, aV_F, $V_{3,4,5,6}$, and there was a general diminution in the voltage of T. The patient was admitted to the hospital and mild angina recurred. The sedimentation rate was 28 mm. per one hour and the transaminase test was 29 units. The patient received 50 mg. of heparin daily. In the early morning of July 3, severe and persistent chest pain developed. An electrocardiogram taken a few hours later revealed an early diaphragmatic wall infarction. The patient required morphine and she was given

150 mg. of heparin twice a day. There was fever, a fall in blood pressure and a moderate degree of leukocytosis. There were basal rales, no gallop rhythm, no venous engorgement, and a roentgenographic study of the chest revealed a minimal pleural reaction at the left side, with normal transparency of the lungfields, and no enlargement of the heart. There was some tenderness in the region of the left costovertebral angle and taking a deep breath was painful. On July 7, the leukocyte count was 11,500 with a shift to the left. There was evidence of *B. coli* infection in the urine. Abnormal neurologic findings appeared on July 16 and the neurologic impression was basilar artery stenosis or insufficiency syndrome. A slight elevation of the temperature persisted. On July 22, the leukocyte count was 9,600 with 2% eosinophils. During the evening of July 22, there developed severe pain on the top of the left scapula which did not radiate. Morphine brought no relief. The pain was aggravated by motion and deep breathing. There was definite tenderness along the ridge of the left scapula, slight pressure discomfort over the upper thoracic spine; there was no evidence for left shoulder involvement. There was no pericardial friction rub. A total of 20 mg. of hydrocortisone was injected subperiosteally at 3 different places along the ridge of the scapula in the afternoon of July 23 and about 20 minutes later the patient felt relieved. Additional improvement took place on applying an ice bag. In the morning of July 24, the temperature was 99° F., there was a slight degree of local throbbing pain; a total of 20 mg. of hydrocortisone was again injected subperiosteally at 3 different places along the ridge of the scapula. By noon the patient was comfortable and the pain did not recur. On July 27, the anticoagulation treatment was changed from heparin to Coumadin and the patient was kept on it permanently. Subsequently the patient did rather well except for fatigability. She did not experience angina and her neurologic status had improved greatly.

COMMENT. The acute chest wall pain started in these 2 patients approximately 6 weeks and 3 weeks, respectively, after the onset of typical myocardial infarction. The degree of pain was severe enough, in both instances, to require the use of an opiate which was not adequately effective. The pain was aggravated by breathing, motion, and decidedly so by local pressure: In the first instance it was localized over the right costochondral junctions and over the left costal arch; in the second instance over the ridge of the left scapula. In both instances there was fever and a moderate degree of leukocytosis. In Case 1 there was eosinophilia on two occasions during the period of pain; in Case 2 there was none when the count was taken prior to the onset of the painful episode.

In Case 1 there was pleurisy, pneumonitis, and pericarditis (to judge by the electrocardiographic alterations); in Case 2 there was highly suggestive evidence for pleural involvement.

In both instances the local subperiosteal injection of 20 mg. of hydrocortisone brought convincing relief. In Case 1, the injections were given on 3 occasions, in the course of 6 days, a total of 100 mg. In Case 2, a total of 40 mg. was used on 2 occasions, in the course of 18 hours.

Case 1, in its entire clinical picture, represents a typical instance of the postmyocardial infarction syndrome, and in Case 2 the findings are compatible with a partial syndrome. This syndrome, as described in recent years by Dressler[1] is a complication that may develop in 3% to 4% of the cases of recent myocardial infarction; it is characterized by fever, chest pain, evidence of pericarditis, pleurisy, and pneumonitis; it has a tendency to recurrences; and it is often mistaken for recurrent myocardial infarction or for pulmonary infarction. Adrenal steroids, or corticotropic hormone, act almost in a specific way. Dressler thought that an antigen produced by myocardial necrosis leads, in susceptible persons, to the formation of autoantibodies. His suggestion is supported by the recent studies of Gery, Davis and Ehrenfeld[3] who demonstrated high

titers of specific heart autoantibodies with the post-myocardial infarction syndrome, recent myocardial infarction, and recent mitral valvotomy.

Our observations indicate that periosteal involvement of chest wall structures can occur, in addition to pneumonitis, pleurisy, and pericarditis, as a part of the post-myocardial infarction syndrome. If present, it either causes a great deal of chest pain, or contributes to chest pain caused by pleural or pericardial involvement, or both. It is readily diagnosed by simple physical examination. The very favorable response to an injection with a corticosteroid favors the concept of an allergic-inflammatory etiology. The presence of eosinophilia during the episode of pain (Case 1) also is in favor of an allergic factor.

It is conceivable that the amount of hydrocortisone injected locally, had also a beneficial effect on the pulmonary-pleural-pericardial manifestations of the syndrome.

The occurrence of chest wall pain subsequent to myocardial infarction, not relieved by nitroglycerin, aggravated by motion and by local pressure, and frequently interpreted by both physicians and patients as cardiac pain, has been described by Edwards[2], and by Prinzmetal and Massumi[4], and the latter authors have reported on the strikingly beneficial effect of corticotropin, cortisone, and radiation therapy.

Conclusion. In 2 cases of recent myocardial infarction, evidence was found for periosteal involvement of chest wall structures, giving rise to pain that was abolished by the local injection of a corticosteroid. This periosteal involvement is thought to be of an allergic-inflammatory origin and represents an addition to the triad of pneumonitis, pleurisy, and pericarditis, that characterizes Dressler's post-myocardial infarction syndrome.

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SUMMARIO IN INTERLINGUA

Dolores Periosteal del Pariete Thoracic Como Parte del Syndrome post Infarcimento Myocardial

In 2 casos de recente infarcimento myocardial, indicationes esseva trovate de un affection periosteal del structuras del pariete thoracic, resultante in dolores que esseva abolite per le injection local de un corticosteroide. Es opinate que iste affection periosteal es de origine allergico-inflammatori e representa un addition al triade de pneumonitis, pleuritis, e pericarditis que characterisa le syndrome de Dressler post infarcimento myocardial.

RIGHT-SIDED BACTERIAL ENDOCARDITIS

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Although bacterial endocarditis most commonly involves the valvular structures on the left side of the heart, about 5% of all cases represent "right-sided" disease (Christian and Middleton[5]) and of these, 73% of the vegetations affect damaged valves or congenital malformations while the remaining cases occur in normal hearts (Barker[3]). The tricuspid valve is commonly involved (Lepeschkin[13]), although overt physical signs suggesting such involvement are frequently lacking (Luttgens[15], Oerting[16]). Blood cultures have been found often to be sterile early in the illness (Blumgart[4]). Systemic embolism is rare, but septic emboli to the lungs resulting in pulmonary infarction with abscess formation and pneumonitis commonly occur (Blumgart[4]).

Materials and Results. Ten adult patients have been studied in whom the diagnosis of right-sided endocarditis was made. Seven of these patients had congenital heart disease. One (Case 1) appeared to have severe pulmonary hypertension and two (Cases 2, 3) had previously normal valves.

All these patients were seen in the interval 1951 to 1959. Despite intensive treatment with antibiotics, 7 died, the diagnoses being confirmed by postmortem examination in 6. In the seventh (Case 4), the diagnosis was suggested by positive blood cultures and multiple pulmonary abscesses in the presence of a patent ductus arteriosus. Of the 3 patients who recovered, one has had corrective heart surgery, and, at the time of operation, areas of scarring consistent with previous bacterial infection were seen (Case 5). The 2 remaining cases are living and well; Case 6 is soon to have corrective surgery. One patient (Case 8) succumbed in her second attack of bacterial endocarditis. At necropsy there were found old healed scars on the tricuspid and the aortic valves, together with small perforations in both of these valves, presumably caused by the first attack of endocarditis 7 years previously.

In the accompanying table, data are given relative to the cardiac disease predisposing to bacterial endocarditis, the predisposing event, and the type of invading organism. In Case 1, moderate thickening and fibrosis of the tricuspid valve was present although the functionally important abnormality was pulmonary hypertension of unknown cause. In Case 2, a moderate thickening of the mitral valve and a slight shortening of the chordae tendinae were suggestive of a healed rheumatic process. In Case 3, the heart valves were normal. In 4 cases, ventricular septal defect alone, or associated with pulmonic stenosis, was present. In Cases 9 and 10, atrial septal defects together with other cardiac anomalies were demonstrated; the vegetative lesions were localized either on the tricuspid or the pulmonary valves, or both.

In 3 patients no predisposing cause was observed. In 2, the procedure of cardiac catheterization was probably instrumental in the production of the disease. In the remaining cases, the invading organism gained entrance into the circulation following normal delivery, dental extraction, septic abortion, genitourinary tract infection and, possibly, a decubitus ulcer. In Case 3, the only blood culture taken during life was sterile, probably

TABLE 1.—FINDINGS IN 10 PATIENTS WITH RIGHT-SIDED BACTERIAL ENDOCARDITIS

Patient	*Associated Cardiac Anomalies*	*Site of Infection*	*Predisposing Event*	*Organism Cultured*	*Functional Heart Class at Onset of Disease*	*Pulmonary Lesion*	*Outcome*
1. D.J.	Pulmonary arterio-and arteriolosclerosis	Tricuspid valve	G.U. tract infection	*Aerobacter aerogenes*	III	Bronchopneumonia	Died, 4th day
2. H.F.	Mitral valve thickened Short chordæ tendinæ	Tricuspid valve	—	Enterococcus	0	Multiple infarcts	Died, 2½ m.
3. S.E.	None	Tricuspid valve	Decubitus ulcer (probable)	None cultured	0	Acute embolic interstitial pneumonitis	Died, 20th day
4. M.X.	Patent ductus arteriosus	P.D.A. (presumed)	Septic abortion	Coagulase + staphylococcus	I	Multiple abscesses and hemorrhage	Died, 20th day
5. C.M.	Ventricular septal defect	On the defect	Dental extraction	*Strep. viridans*	II	Infiltrates	Recovered
6. A.O.	Ventricular septal defect Pulmonic stenosis	—	—	*Strep. viridans*	II	Infiltrates	Recovered
7. V.R.	Ventricular septal defect	—	Normal delivery	*Strep. viridans*	I	Abscess	Recovered
8. S.G.	Ventricular septal defect	Septal defect Tricuspid valve	1st (1952) Septic abortion	*Strep. viridans*	I	—	Recovered
		Aortic valve	2nd (1959) None:	Enterococcus	I	Hematogenous pneumonia	Died, 3rd day
9. M.L.	Atrial septal defect Anomalous pulmonary venous drainage	Tricuspid and pulmonary va'ves	Heart catheterization (infected site)	Coagulase + staphylococcus	III	Multiple infarcts Large embolus	Died, 6th day
10. J.D.	Pulmonary stenosis Corrected transposition of great vessels Atrial septal defect	Pulmonary valve	Heart catheterization; angiocardiography	None cultured	IV	Infarcts, emboli	Died, 8th day

because antibiotic drugs had already been given. At necropsy the vegetations were not cultured. In Case 10, multiple blood cultures during life and cultures of vegetations at necropsy were sterile. The vegetations in Case 3 and Case 10 showed coccal forms on microscopic examination, and the clinical courses suggested that the organism in each case was a staphylococcus that had been suppressed, especially in the latter case, by massive antibacterial treatment. If this is so, then 4 of the cases were due to staphylococci and were acute in nature, while one was due to *Aerobacter aerogenes*, 2 to enterococci, and 3 to *Streptococcus viridans*.

The only patients of this series that recovered were those with *Streptococcus viridans* infections that were clinically and bacteriologically sensitive to penicillin. Four of the patients who died did so within a few days after the institution of treatment. In all patients, pulmonary complications were instrumental in the fatal outcome.

Case Report. CASE 4. An 18-year-old woman developed foul vaginal discharge following spontaneous abortion 3 months prior to admission. A month later she experienced recurrent episodes of chills and fever for which she received intensive antibiotic therapy for one month.

A few days prior to admission, the fever and chills recurred, and were associated with a right pleuritic chest pain. The cough was productive; the sputum was mucopurulent and blood-streaked. The patient had had no cardiac symptoms. A heart murmur was noted in early childhood. She had 2 normal deliveries prior to this illness.

The patient looked emaciated and pale. There were two petechiae on the hard palate. The conjunctivae and fundi were normal. The blood pressure was 110/55 mg. Hg. The neck veins were flat. Moist crepitant rales were heard over both lungs. The heart was not enlarged. A continuous thrill was felt over the left second and third intercostal spaces and a machinery murmur was present at this level. The tip of the spleen was felt. The rest of the physical examination was normal.

The hemoglobin level was 8.0 to 8.6 gm. per 100 ml. The total leukocyte count varied between 19,000 to 12,000 per ml. with 85 to 90% polymorphonuclears. The blood urea nitrogen was 42 mg. per 100 ml. The urine showed a trace of albumin, numerous red blood cells and granular casts in the sediments. Three blood cultures grew *Staphylococcus aureus* (coagulase positive) sensitive to erythromycin, Cathomycin and chloramphenicol. Gram stain of the sputum showed numerous Gram-positive cocci in chains and diplococci. The electrocardiogram revealed nonspecific T wave changes. A chest film demonstrated multiple bilateral pulmonary abscesses. The heart was not enlarged, but the pulmonary artery segment and the peripheral pulmonary vessels were prominent (Fig. 1).

The patient was given 2.5 gm. erythromycin and 15 million units of penicillin daily. On the 4th day she experienced sudden severe right-sided chest pain and became hyperpneic. The pain was pleuritic in nature. On the 5th day paralytic ileus appeared. Cathomycin and streptomycin, each 2 gm. daily, were added. She subsequently improved and by the 11th day her temperature dropped to normal. Repeated blood cultures were sterile. The blood urea nitrogen dropped to 22 mg. per 100 ml. and her urinary sediment contained fewer red blood cells. Between the 11th and 15th days, the patient developed two such episodes of chest pain exaggerated by inspiration. All through her hospitalization, the patient had blood-streaked expectoration. She recovered from those incidents and while being prepared with transfusions for surgical ligation of the patent ductus arteriosus, she suddenly complained of nausea, had profuse hemoptysis and expired. Postmortem examination was denied.

The final episode was most probably caused by a ruptured pulmonary vessel; however, a massive infarct could not be ruled out. The patient presumably had a patent ductus arteriosus, a superimposed bacterial endocarditis with multiple pulmonary emboli, small abscess formation and most likely, systemic embolization.

Discussion. There has been much speculation about the relative immunity of the right side of the heart to bacterial infection. This could not be explained by the property of its endocardium, which is identical to that on the left side, but perhaps the most significant factor is the relatively low pressure existing in its chambers (Lepeschkin[13]).

Clinically in humans, as well as experimentally in dogs, it has been observed that trauma, in the form of pressure or stress, may be the sole factor responsible for the production of bacterial endocarditis. Cardiovascu-

lar stress, in the form of arteriovenous fistulas, is known to increase the susceptibility of the endocardium to bacterial infection (Gowdy *et al.*[11], Lillehei *et al.*[14], Rabens *et al.*[18]). The presence of endocardial fibrosis, the so-called "jet" lesion of ventricular defect or aortic coarctation, likewise increases the chance of bacterial infection and the jet lesion itself may be the site of infection (Dalous, Fabre and Pons[6], Eigen and Abel[7], Gordon and Perla[10]). It has also been noticed that vegetations tend to occur on the valve surface facing the chamber being served, suggesting that pressure alone may be a factor (Allen[1]). This observation is confirmed by the rarity of bacterial endocarditis on the septal defect in simple and complicated atrial septal defect (Sussman and Price[20]). In both patients (Cases 9 and 10) with atrial septal defect, the defect was free of vegetations. The vegetations in these cases were localized either on the tricuspid or pulmonary valves or both.

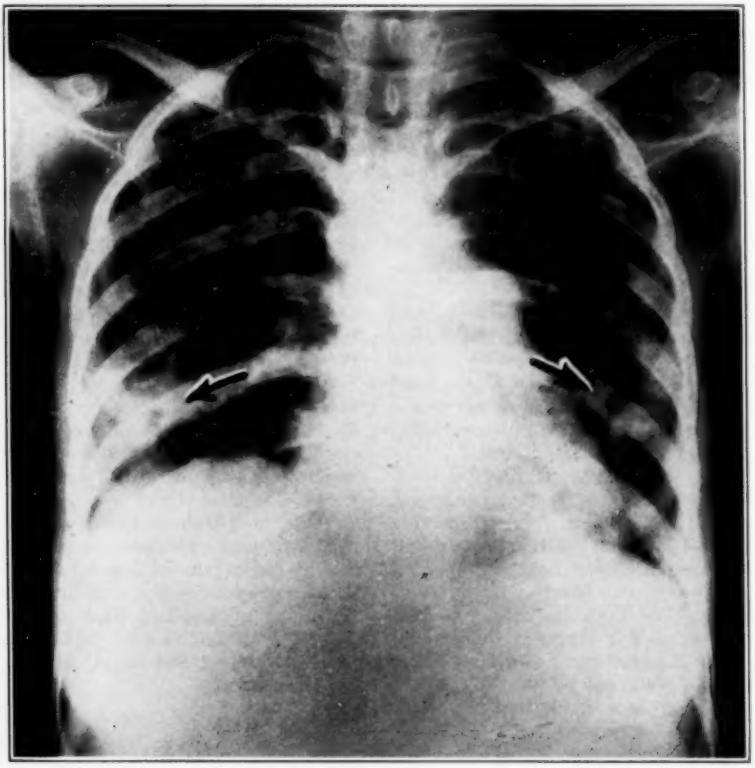

Fig. 1.—Case 4. Chest film shows the bilateral pulmonary abscesses. The pulmonary infiltrate is most marked over the right lung field. The pulmonary artery segment is prominent.

Three patients (Cases 1, 2, and 3) had bacterial endocarditis in the absence of a congenital heart lesion, an incidence similar to that reported in Barker's series[3]. In Case 1, valvular trauma, in the form of right-sided hypertension, was probably the factor responsible for the production of

endocarditis. This patient had electrocardiographic findings of right ventricular preponderance, and, at necropsy, pulmonary atherosclerosis and arteriosclerosis, implying the existence of pulmonary hypertension during life. In Cases 2 and 3, there was no clinical or necropsy evidence of a pre-existing pulmonary hypertension and the infection occurred on valves previously normal. Normal right heart valves are known to become infected if the organism concerned is highly virulent and if it is present in the blood in large numbers (Goldburgh, Baer and Lieber[9], Hussey and Katz[12], Preble[17]).

Prior to the use of penicillin, most cases of bacterial endocarditis in congenital heart disease were caused by *Streptococcus viridans* (Seabury[19]), but in recent years other organisms, especially staphylococci, have become much more common. It is apparent that from the cases herein reported that events ordinarily benign such as heart catheterization or normal obstetrical delivery may have been the source of bacterial infection. Skin infections may also provide the organism responsible for bacterial endocarditis (Bain *et al.*[2]).

Four of the 7 patients who died did so 3 to 8 days from the onset of the disease and after onset of antibiotic therapy. The pulmonary lesion was thought to be the main single factor responsible for their demise. In this regard, the other 3 patients who died were of special interest. Cases 2 and 4 succumbed to the disease after sterilization of their blood stream. Multiple focal pulmonary emboli and infarctions were demonstrated at postmortem examination in Case 2; however, Case 4 expired suddenly following a profuse pulmonary hemorrhage. Case 3 had developed a cerebrovascular accident, a decubitus ulcer and a probable aspiration pneumonia. He died subsequently on the 20th hospital day and at necropsy acute embolic interstitial pneumonitis was observed.

Despite the fact that the right side of the heart was primarily infected, positive blood cultures were obtained in 8 of our cases. In all, the organism was recovered early in the illness. This is contrary to previous reports (Blumgart[4]) and to the idea that the lungs act as bacterial filters.

That a patient may develop a second episode of bacterial endocarditis with a virulent organism after recovery from the first is illustrated in Case 8. It is essential therefore in these patients that any anomaly amenable to surgery be corrected.

Summary. Ten patients with right-sided bacterial endocarditis have been observed since 1951. In 8, positive blood cultures were obtained early in the disease. The recovered organisms were *Streptococcus viridans* in 3, enterococcus in 2, *Staphylococcus aureus* in 2, and *Aerobacter aerogenes* in one. In 2, no organism could be cultured.

In the 3 patients who recovered, the responsible organism was *Streptococcus viridans* sensitive to penicillin. In the remaining 7 who succumbed, pulmonary involvement was thought to be the main factor responsible for death.

Three patients developed the disease in the absence of congenital heart lesions; in 2, the affected valves were presumably normal and in one, idiopathic pulmonary hypertension was present. Intracardiac trauma, especially in the form of increased pressure, and virulence of the invading organism are the important factors in the production of right-sided endocarditis.

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SUMMARIO IN INTERLINGUA

Endocarditis Bacterial Dextero-Lateral

Depost 1951, 10 patients con endocarditis bacterial dextero-lateral ha essite observate. In 8, positive culturas de sanguine esseva obtenite precocemente in le curso del morbo. Le organismos identificate esseva *Streptococcus viridans* in 3, enterococcos in 2, *Staphylococcus aureus* in 2, e *Aerobacter aerogenes* in un. In 2, nulle organismo poteva esser culturate.

In le 3 patientes qui se restabliva, le organismo responsabile esseva *Str. viridans* (que es sensibile a penicillina). In le 7 qui moriva, le affection del pulmon esseva considerate como principalmente responsabile pro le morte.

Tres del patientes contraheva le morbo in le absentia de congenite lesiones cardiac. In 2, le afficite valvulas esseva presumitemente normal. In un, idiopathic hypertension pulmonar esseva presente. Trauma intracardiac, specialmente in le forma de augmento del tension, e virulentia del organismo invadente es le importante factores in le production de endocarditis dextero-lateral.

HYDROCHLOROTHIAZIDE USED ALONE IN CONGESTIVE HEART FAILURE AND IN COMBINATION WITH PREDNISONE AND OTHER DIURETICS IN CIRRHOSIS AND NEPHROSIS*

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Hydrochlorothiazide (Ford, Moyer and Spurr[14]) was introduced soon after chlorothiazide (Richterich[33]). When this dihydrogenated derivative (Fig. 1) was tested in the laboratory and used in preliminary clinical trials, it caused less potassium loss than chlorothiazide (Meciani and Brina[22], Ford[12], Cassano *et al.*[5]). Otherwise, the diuretic action of hydrochlorothiazide paralleled that of the parent compound, consisting mainly of inhibition of tubular resorption of sodium and chloride and resembling that of the mercurial diuretics (Ford[12], Cassano *et al.*[5], Hejtmancik, Herrmann and Kroetz[15], Mertz and Schettler[23]). Clinically, hydrochlorothiazide has been effective in relieving various types of edematous conditions such as those accompanying congestive heart failure (Cassano *et al.*[5], Platts[28], Brest and Likoff[2], Nicolay[25], Keller[16]), nephrosis (Nicolay[25], Keller[16]), and cirrhosis (Cassano[5], Losse *et al.*[19], Rissel *et al.*[34]). In cirrhotic patients one advantage of the use of hydrochlorothiazide is that, unlike chlorothiazide or acetazolamide, it does not elevate the blood ammonia (Mertz and Schettler[23], Rissel *et al.*[34]). This may be due to its lower carbonic anhydrase inhibiting action (Barrett *et al.*[1]). Both the reduced kaliuretic effect and the unaltered blood ammonia

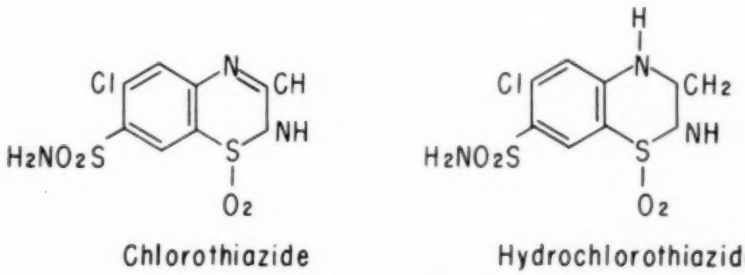

Fig. 1.—Structural formula of hydrochlorothiazide.

*Aided by a grant for study on new diuretic agents through courtesy of C. H. Sullivan, M.D., Ciba Pharmaceutical Products, Inc., Summit, N.J.

level suggest hydrochlorothiazide as a desirable diuretic for treating decompensated cirrhosis. In nephrosis with salt and water retention, combination of hydrochlorothiazide with prednisone results in a profound diuresis (Nicolay[25]).

The chief restrictions to the use of chlorothiazide are states of sodium or potassium depletion, or depletion of both (Keller[16]). Whether or not an increased blood urea nitrogen contraindicates its use is open to question (Mertz and Schettler[23], Brest and Likoff[2]).

The present report deals with the clinical trial of hydrochlorothiazide* in hospitalized patients. The study was designed to evaluate the response to this new diuretic when used alone or when administered initially and then supplemented with prednisone and other diuretics in patients with congestive heart failure, cirrhosis and nephrosis. To our knowledge the use of prednisone in conjunction with hydrochlorothiazide in the treatment of cirrhosis has not been reported previously.

Methods and Materials. PATIENTS. The 20 patients included in this study were divided into 2 groups. Eleven patients in Group I had congestive heart failure. Of the 9 patients in Group II, 8 had edema due to cirrhosis and one due to nephrosis. The Group II patients were evaluated separately since the etiologic cause of their salt and water retention presented a more difficult problem from the standpoint of diuretic therapy. Six of these patients had responded poorly to initial therapy with hydrochlorothiazide; consequently, alternate forms of diuretic therapy were then tried with or without hydrochlorothiazide.

The 12 men and 8 women averaged 59.4 years (range 38 to 85 years) in age. All had been hospitalized because of the severity of their edema or ascites, or both. The average duration of hydrochlorothiazide administration was 13.5 days (range 5 to 40 days). Table 1 lists the diagnoses, treatment, and urinary responses for these 20 patients.

PROCEDURE. When admitted, patients were placed at bed rest, given a 1 gm. sodium diet, and, if indicated, digitalized or continued on maintenance digitalis. No fluid restriction was employed; however, the average fluid intake varied between 1500 and 2000 ml. per day. A 3-day "control" period was allowed for stabilization before starting trial of hydrochlorothiazide.

Daily determinations of body weight, blood pressure, urinary volume, urinary electrolytes and urinary pH were made during both the control and treatment period. Serum electrolytes and bicarbonate were determined bi-weekly and the blood urea nitrogen and the hemogram obtained once a week.

DIURETIC THERAPY. Following the initial 3-day stabilization period, patients were started on 50 mg. of hydrochlorothiazide orally, given three times daily after meals. After 4 to 6 days, 5 patients in Group II received a dosage increase to 75 mg. three times a day while 2 of these patients subsequently were given 100 mg. thrice daily. Four of these 5 patients later had prednisone added to their regimen. Prednisone was employed in a dosage of 10 mg. every 8 hours and continued until maximum therapeutic benefit was achieved. In 2 patients prednisone was discontinued after 3 and 5 days, respectively, since only a transient enhancement of sodium and water diuresis occurred. Acetazolamide was used in 3 patients of Group I who showed elevated serum bicarbonate levels at the conclusion of hydrochlorothiazide trial.

After initial trial of hydrochlorothiazide, chloride loading was accomplished in 6 Group II patients by using either 30 ml. of 10% calcium chloride solution in 120 ml. of dietetic tomato juice four times a day, or, on alternate days, with 2 gm. of potassium chloride given three times a day. This was done for a minimum of 3 days and a maximum of 5 days. On the last day of chloride administration, 2 ml. of meralluride were administered intramuscularly and then repeated 48 hours later. Calcium or potassium salts were used, rather than ammonium salts, because of the presence of liver disease in these patients. The 48-hour interval between the mercurial injections insured complete tissue clearance of the drug (Pitts[26]). Another regimen tried in 3 cirrhotic patients was administration of hydrochlorothiazide, 50 mg. three times a day, alternated every other day with acetazolamide, 250 mg. twice a day. Finally, 3 of the cirrhotic patients and the

*Esidrix is the trade name of the hydrochlorothiazide (dihydro form of chlorothiazide) used in this study.

TABLE 1.—DIAGNOSES, DIURETIC THERAPY, AND CHANGES IN URINARY AND SERUM ELECTROLYTES IN 20 PATIENTS TREATED WITH HYDROCHLOROTHIAZIDE

					Response To Hydrochlorothiazide				
					Average Weight loss				
Patient No.	*Age (yrs.)*	*Sex*	*Dose (mg. per day)*	*No. Days Given*	*Total (lbs.)*	*Per Day (lbs.)*	*Urinary Electrolytes*	*Serum Electrolytes*	*Response*	*Other Diuretics*
Group I, Congestive Heart Failure										
1	67	M	150	6	5	0.8	Initial transient natruresis	Increased bicarbonate	Good	Acetazolamide on 7th day.
2	67	F	225	7	11	1.6	Natruresis; moderate kaliuresis	Increased bicarbonate	Good	Acetazolamide on 8th day.
3	66	M	150	12	18	1.5	Diuresis and saluresis; moderate kaliuresis	Not determined	Excellent	
4	78	F	150	14	—	—	Natruresis and kaliuresis	Chloride decrease of 8 mEq./L.	Excellent	
5	60	M	150	7	21	3.0	Marked saluresis	No change	Excellent	
6	79	F	150	10	6	0.6	Saluresis; moderate kaliuresis	Increase in blood urea nitrogen and bicarbonate	Fair	
7	62	F	150 225	7 5	8	0.8	Natruresis	Low potassium on admission, required potassium supplement	Fair	
8	58	M	150	12	16.5	1.4	Saluresis	No change	Good	
9	85	M	150	5	15	2.5	Saluresis; significant kaliuresis	Moderate increase in blood urea nitrogen	Excellent	Acetazolamide on 13th day.

TABLE 1.—DIAGNOSES, DIURETIC THERAPY, AND CHANGES IN URINARY AND SERUM ELECTROLYTES IN 20 PATIENTS TREATED WITH HYDROCHLOROTHIAZIDE—*Continued*

							Response To Hydrochlorothiazide			
					Average Weight loss					
Patient No.	*Age (yrs.)*	*Sex*	*Dose (mg. per day*	*No. Days Given*	*Total (lbs.)*	*Per Day (lbs.)*	*Urinary Electrolytes*	*Serum Electrolytes*	*Response*	*Other Diuretics*
10	61	M	150	14	22	1.6	Not determined	Potassium decreased 1.5 mEq./L.	Good	
11	61	M	150	4	7	1.8	Increased saluresis; significant potassium loss	Elevated blood urea nitrogen unchanged	Excellent	
Group II, Cirrhosis										
12	55	M	150 225	3 40	0	0	No change	Increased bicarbonate with added prednisone and acetazolamide	Failure	Hydrochlorothiazide, 75 mg. t.i.d. alternated with acetazolamide b.i.d. from 6th to 20th day; prednisone, hydrochlorothiazide from 21st. to 43rd. day
13	55	M	150 225	5 17	16.5	0.8	No change	Sodium decrease with added meralluride	Fair	Good response first 6 days; refractory to added meralluride on 8th day and to prednisone from 10th to 20th day (Meralluride with chloride loading after hydrochlorothiazide)
14	38	F	150	6	10	1.7	Marked saluresis and moderate kaliuresis	No change	Excellent	

15	45	M	150 225 300	5 5 6	2	0.2	Moderate natruresis with added prednisone and acetazolamide; maximal saluresis day after (10th day) therapy stopped	Sodium and potassium decrease during added acetazolamide therapy	Fair	Acetazolamide alternated with hydrochlorothiazide first 5 days of trial; prednisone added 11th to 13th day (Meralluride with chloride loading after hydrochlorothiazide)
16	47	F	150	8	2	0.3	Sustained natruresis; potassium loss in excess of supplemental potassium intake	No change	Fair	Acetazolamide alternated with hydrochlorothiazide 1st 4 days; meralluride with chloride loading after hydrochlorothiazide
17	55	M	150 225 300	5 5 5	1 0 0	0.2 0 0	No change	No change	Failure	Meralluride on 4th day; prednisone added on 6th day and stopped on 11th day
18	51	F	100	11	29	2.6	Marked saluresis	Lowered bicarbonate due to prior acetazolamide therapy	Excellent	
19	61	M	150 225	3 4	12	1.7	Sustained saluresis; potassium loss in excess of intake last 4 days of therapy	Significant decrease in potassium	Good	Meralluride on 4th and 7th day; chloride loading and meralluride on 4th and 8th days after hydrochlorothiazide
Group III, Nephrosis										
20	43	F	150	22	13½	0.6	Marked saluresis with added prednisone; with prednisone alone, no change from control	Slight decrease bicarbonate with added acetazolamide	Satisfactory	Chloride loading and meralluride on 8th and 10th days; "excellent" response with prednisone added from 11th to 22nd day. Prednisone continued from 23rd to 27th day

one nephrotic who had been receiving only hydrochlorothiazide, were given an injection of meralluride on every fourth day during the trial period. It was hoped that using meralluride and hydrochlorothiazide in combination, would provide a more effective enzymatic blocking of the proximal tubule and, therefore better diuresis.

Results. RESPONSES. Patient responses during hydrochlorothiazide therapy were graded on the basis of weight loss and excretion of urinary sodium compared to control values. When the weight loss was over 2 pounds a day, or there was a greater than a two-fold increase in urinary sodium, or both occurred, the response was considered excellent. A good response was reported when the weight loss was between 1 and 2 pounds a day, or there was a one- to two-fold increase in urinary sodium, or both occurred. Patients losing between one-half and one pound of weight and excreting at least one-half again the control level of sodium each day were placed in the satisfactory category. Patients not grouped into one of these three categories were considered therapeutic failures; all of the therapeutic failures were Group II patients who had cirrhosis or nephrosis.

BODY WEIGHT. The average weight loss resulting from bed rest and low salt intake during the stabilization period was 0.6 pounds per day for these 19 patients. During hydrochlorothiazide therapy 16 patients showed some weight loss, 10 of whom lost more than 1 pound per day (Table 2). The 3 patients who failed to show any weight loss were confined to Group II. The maximum average weight loss for all types of therapy used in this study amounted to 1.6 pounds per day and occurred in the Group I patients given only hydrochlorothiazide. The average weight loss for the entire series was 1.1 pounds per day. The one patient who could not be weighed because of an acute myocardial infarction demonstrated an excellent natruretic response with rapid clearing of peripheral edema.

When prednisone was added to hydrochlorothiazide in 4 cirrhotic patients and 1 nephrotic patient, increased weight loss occurred in 3 (Table 3). Because of the improvement noted in the nephrotic patient (Case 20), her response was upgraded from that of satisfactory, for hydrochlorothiazide alone, to excellent.

URINARY VOLUME AND ELECTROLYTES. With hydrochlorothiazide the urinary volume was increased an average of 50% with the major increase observed in the Group II patients. In the 5 patients who received concomitant hydrochlorothiazide-prednisone therapy, a two-fold increase in urinary volume resulted.

The sodium excretion amounted to at least twice the control value in 13 patients given hydrochlorothiazide only (Table 4). In 5 other patients the natruresis more than tripled the control values. Three of these 5 patients were cirrhotics while the other 2 had had an extremely low output of urinary electrolytes before treatment.

Urinary potassium excretion was increased on the average by one-third the control level in the 12 patients with congestive heart failure. Four of these patients had an increase in potassium loss between one and two times the control value, in another the increase amounted to one-half the control value, while in the other 7 patients potassium loss was relatively unchanged. These patients were not given supplementary potassium during trial of hydrochlorothiazide.

When alternate forms of diuretic therapy were tried in the Group II patients, both prednisone-hydrochlorothiazide (Table 5) and hydrochlorothiazide-meralluride produced the most

TABLE 2.—EVALUATION OF RESPONSE TO HYDROCHLOROTHIAZIDE AND OTHER DIURETICS ON BASIS OF WEIGHT LOSS IN 19 PATIENTS

Diuretic Drugs Administered	*Group Number*	*Number of Patients*	*Average Weight Loss per day (lbs.)*	*Response Classification on Basis of Weight Loss Number of Patients*			
				Excellent (Loss of 2 lbs. or more per day)	*Good (1–2 lb. loss per day)*	*Satisfactory (Loss of 0.5 to 1 lb. per day)*	*Failure (Less than 0.5 lb. loss per day)*
Control	1	10	0.9	1	2	3	3
	2	9	0.4	0	2	2	5
	1 + 2	19	0.6	1	4	5	8
Hydrochlorothiazide	1	10	1.6	2	5	3	0
	2	9	0.6	1	2	2	4
	1 + 2	19	1.1	3	7	5	4
Acetazolamide	1	3	0.9	0	2	1	0
Hydrochlorothiazide plus prednisone.	2	5	0.5	1	0	3	1
Chloride loading and meralluride.	2	6	0.9	1	2	3	1
Hydrochlorothiazide alternated with acetazolamide.	2	4	0.6	–	–	1	3
Hydrochlorothiazide plus meralluride	2	4	1.1	1	2	1	–

striking urinary salt and water elimination. These patients received potassium chloride supplements. In only one patient did the kaliuresis exceed the amount of potassium ingested.

SERUM ELECTROLYTES. No significant changes were noted in the serum electrolytes except for elevation of the bicarbonate in 3 of the Group I patients (Table 4). All responded to acetazolamide.

The blood urea nitrogen increased an average of 6 mg. per 100 ml. in the Group I patients during hydrochlorothiazide treatment. No patient had a blood urea nitrogen greater than 45 mg. per 100 ml. and no correlation existed between the blood urea nitrogen level and the predictability of the patient's diuretic response.

BLOOD PRESSURE. Only 1 patient had a diastolic blood pressure greater than

TABLE 3.—WEIGHT LOSS IN 4 CIRRHOTIC AND 1 NEPHROTIC PATIENT DURING HYDROCHLOROTHIAZIDE-PREDNISONE TREATMENT

Case	*Diagnosis*	*Weight Loss (Aver.)*		*Treatment Period (days)*
		Control (lbs./day)	*Treatment (lbs./day)*	
12	Cirrhosis	0	0.36	22
13	Cirrhosis	0.1	0.62	10
15	Cirrhosis	0.2	0.3	3
17	Cirrhosis	0.2	0	5
20	Nephrosis	0.1	1.7	11
	Aver.	0.1	0.6	9

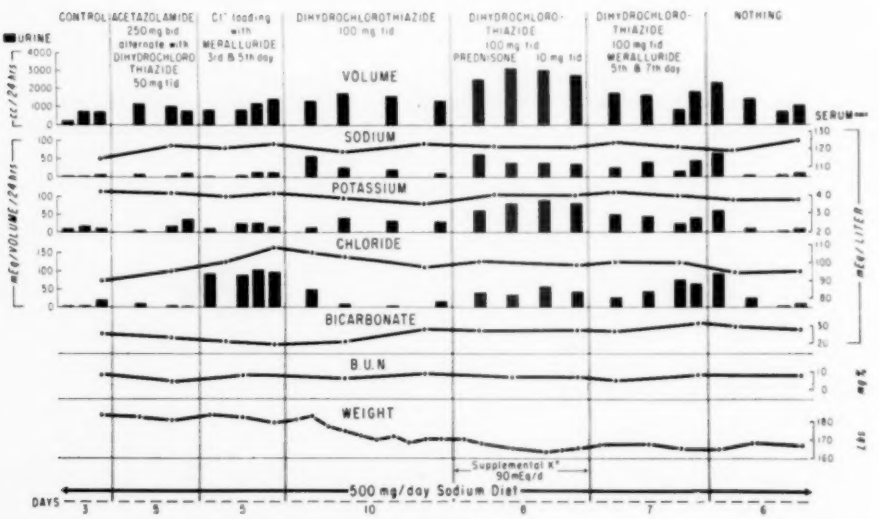

Fig. 2.—(Case 13). Changes in urinary volume, urinary and serum electrolytes, blood urea nitrogen during treatment with hydrochlorothiazide and other forms of diuretic therapy (the designation of dihydrochlorothiazide used in this graph was that originally used for hydrochlorothiazide).

TABLE 4.—THE AVERAGED URINARY VOLUMES, URINARY ELECTROLYTES AND SERUM ELECTROLYTES DURING TREATMENT WITH HYDROCHLOROTHIAZIDE AND OTHER DIURETICS COMPARED WITH AVERAGES FOR THE 3-DAY CONTROL PERIOD

			Urinary Excretion												
					Electrolytes (mEq./24 hr.)						*Serum Electrolytes (mEq./L.)*				
			Volume (ml./24 hr.)		*Sodium*		*Potassium*		*Chloride*						*Blood Urea Nitrogen (mg./100 ml.)*
Treatment	*Group No.*	*No. of Patients*	*Total*	*Increase*	*Total*	*Increase*	*Total*	*Increase*	*Total*	*Increase*	*Sodium*	*Potassium*	*Chloride*	*Bicarbonate*	
Control	I	11	1075		30.2		32.5		74.6		125.7	3.9	99	25.9	16
	II	9	1000		20.6		45.4		24.9		125.7	4.4	98.4	23.4	12.7
	I‡ II	20	1045		37		38.3		52.3		125.7	4.2	98.8	24.8	14.5
Hydrochlorothiazide	I	11	1160	85	86.1	35.9	44.7	12.2	80	5.4	125.1	4.2	97.3	25.5	22.3
	II	9	1785	785	80.0	59.4	N.S.*		111.3	86.4	121.4	3.9	97	24.2	13.3
	I‡ II	20	1455	410	83.2	46.2	N.S.*		94.8	42.5	123.5	4.1	97.2	24.9	18.2
Acetazolamide	I	3	1325	250	31	19.2†	42	9.5	32	42.6†	124.7	4	95.7	29.3	11.7
Hydrochlorothiazide and prednisone	II	5	2305	1350	69	48.4	N.S.*		42.4	17.5	122.8	3.7	94.6	26.5	11
Chloride loading with meralluride	II	6	1665	665	64	43.4	N.S.*		143‡	98.1‡	120.3	4.2	103.1	21.4	17.1
Hydrochlorothiazide alternated with acetazolamide	II	4	1340	340	40.5	19.9	N.S.*		35.8	9.6	125.5	3.6	102	22	12
Hydrochlorothiazide with meralluride	II	4	1925	925	125	104.4	N.S.*		158.8	133.9	124.5	3.4	105	21.8	24.5
Difference, hydrochlorothiazide and control	I	11	1.1 (ratio)		1.65 (ratio)		1.33 (ratio)		1.1 (ratio)						
	II	9	1.78 "		4 "		N.S.* "		4.5 "						
	I‡ II	20	1.4 "		2.3 "		N.S.* "		1.8 "						
							N.S.* "		1.7 "						
Difference, hydrochlorothiazide-prednisone and control.	II	5	2.2 "		3.35 "										

N.S.* Not significant due to use of supplemental potassium
† Decrease
‡ Due to chloride loading

90 mm. of mercury; with hydrochlorothiazide the diastolic pressure fell 10 mm. of mercury.

Case Histories. The individual responses for 2 cirrhotic patients, Case 13 and Case 14, who required alternate forms of diuretic therapy including a combination of prednisone and hydrochlorothiazide, are shown in Figs. 2 and 3.

Fig. 2. With continuation of hydrochlorothiazide for 7 days and injections of meralluride on the fifth and seventh day, other than some saluresis following the meralluride, no significant changes were noted.

Two months after discharge the patient was seen in the outpatient division and found to have returned to his pre-hydrochlorothiazide-prednisone treatment state. Interval therapy had consisted of salt restriction, frequent rest periods and chlorothiazide with potassium supplementation.

TABLE 5.—COMPARISON OF URINARY VOLUME AND ELECTROLYTE EXCRETION IN 5 PATIENTS TREATED WITH HYDROCHLOROTHIAZIDE AND HYDROCHLOROTHIAZIDE-PREDNISONE.

	Urinary Excretion			
		Electrolytes (mEq./24 hr.)		
Treatment	*Volume (ml./24 hrs.)*	*Sodium*	*Potassium*	*Chloride*
Control	795	13	16.6	10
Hydrochlorothiazide	970	11	N.S.*	8.6
Hydrochlorothiazide and prednisone	2305	69	N.S.*	42.4
Ratio, Hydrochlorothiazide to control	(1.2)	(0.85)		(0.85)
Ratio, Hydrochlorothiazide to prednisone	(2.7)	(5.3)		(4.12)

N.S.*—Not significant due to supplemental potassium.

Case Reports. CASE 13 (Fig. 2). A 55-year-old white man with a long history of alcoholism complicated by the presence of Laennec's cirrhosis. Because of poor hepatic compensation for the past 3 years he had required frequent hospitalization. During his present admission both ascites and pedal edema were present although there was no evidence of hepatic precoma. Following a 3-day stabilization period, he was given acetazolamide and hydrochlorothiazide on alternate days for 5 days, followed by 5 days of chloride loading and injections of meralluride on the third and fifth days. Other than some chloruresis, no significant response was noted. He was then continued on hydrochlorothiazide for 10 days with some improvement in his condition and weight loss. However, the persistence of ascites and edema, plus the "leveling off" noted during the last 4 days of this treatment prompted the addition of prednisone. The enhanced urinary output of both sodium and water, along with further weight loss, is strikingly shown in

CASE 15 (Fig. 3). A 45-year-old white man with alcoholic cirrhosis had had symptoms for over 6 years. Past history included a previous admission to this hospital 18 months ago because of hepatic decompensation manifested by excess salt and water retention and early evidence of hepatic precoma. Present admission was necessitated by similar complications with the signs of precoma being minimal. As shown in the Fig. 3, a variety of diuretic approaches were employed without satisfactory results. Prednisone was added to hydrochlorothiazide for 3 days and then withdrawn since only transient improvement in the diuretic response was noted.

Discussion. The various clinical procedures employed in this study for the evaluation of a new diuretic provide useful information and appear practicable. Allowance of an initial 3-day stabilization period removes the in-

fluence of bed rest, salt free diet and digitalization as variables when trial of the diuretic drug is started. Also, the initial stabilization period permits each patient to serve as his or her own control. When patients with congestive heart failure are put to bed the average control urinary responses and weight losses are usually higher than Johnson[20], Dyrenfurth *et al.*[10], Chart and Shipley[7], Wolff *et al.*[39]).

Table 6 was prepared in order to correct the over-weighted influence of the control period averaged results for urinary excretion when compared with those obtained during trial of hydrochlorothiazide. By using only the third day results of the stabilization period as

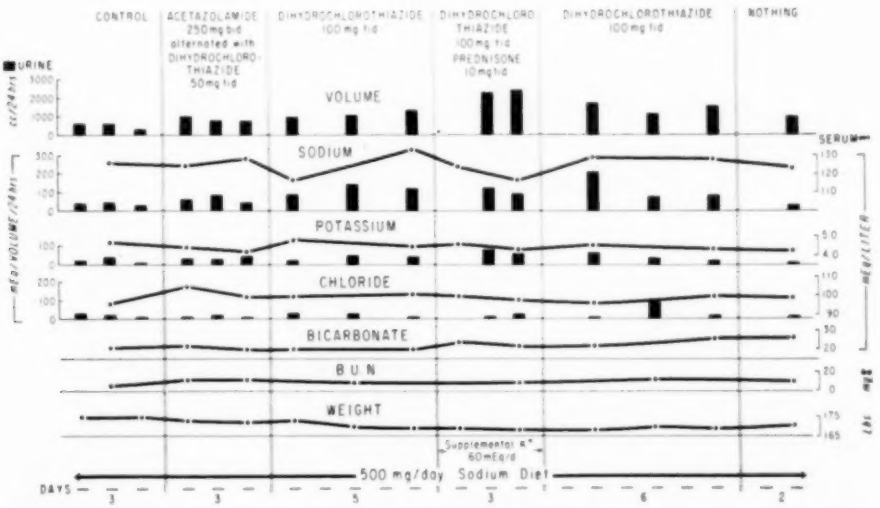

Fig. 3.—(Case 15). Changes in urinary volume, urinary and serum electrolytes, blood urea nitrogen during treatment with hydrochlorothiazide and other forms of diuretic therapy (the designation of dihydrochlorothiazide used in this graph was that originally used for hydrochlorothiazide).

normally expected because of the enhanced urinary output. Subsequently, the response to hydrochlorothiazide administered after the 3-day control period, appears less dramatic. Despite this apparent discrepancy, which is inherent in the method of study employed here, a more realistic report of the drug's true effectiveness is obtained. In several cirrhotic patients the pre-treatment excretion of sodium was abnormally low. This may have been due to excessive aldosterone secretion which occurs in advanced states of decompensated cirrhosis (Luetscher and a baseline, a proportionate increase in the net difference of the various responses is registered in all parameters measured. The greatest gain was in urinary volume. When the weight loss during the control period is compared to that of hydrochlorothiazide therapy, any therapeutic response less than the control average would seem insignificant. This is not true. With bed rest, maximum diuresis is reached by the third day and, beyond this time, the diuresis rapidly dissipates. These observations are based on the results of a study one of us (G.A.P.) made on

TABLE 6.—THE AVERAGED URINARY VOLUMES AND ELECTROLYTES DURING TREATMENT WITH HYDROCHLOROTHIAZIDE AND OTHER DIURETICS COMPARED WITH AVERAGES FOR THE THIRD DAY OF THE CONTROL PERIOD

			Urinary Excretion							
			Volume (ml./24 hr.)		*Electrolytes (mEq./24 hr.)*					
					Sodium		*Potassium*		*Chloride*	
Treatment	*Group No.*	*No. of Patients*	*Total*	*Increase*	*Total*	*Increase*	*Total*	*Increase*	*Total*	*Increase*
Control	I	11	930		55.5		22.3		70.3	
	II	9	775		13.4		12.2		9	
	I ‡ II	20	860		36.6		17.8		42.7	
Hydrochlorothiazide	I	11	1160	230	86.1	30.6	44.7	22.4	80	9.7
	II	9	1785	1010	80	66.6	N.S.*	—	111.3	102.3
	I ‡ II	20	1455	595	83.2	46.6	N.S.*	—	94.8	52.1
Acetazolamide	I	3	1325	395	31	24.5†	42	19.7	32	38.3†
Hydrochlorothiazide and prednisone	II	5	2305	1530	69	55.6	N.S.*	—	42.4	33.4
Chloride loading with meralluride	II	6	1665	890	64	50.6	N.S.*	—	143‡	134
Hydrochlorothiazide alternated with acetazolamide	II	4	1340	565	40.5	27.1	N.S.*	—	35.8	26.8
Hydrochlorothiazide with meralluride	II	4	1925	1150	125	111.6	N.S.	—	158.8	149.8
Ratio, hydrochlorothiazide to control	I	11	1.3		1.6		2		1.1	
	II	9	2.3		6		N.S.*		12.2	
	I ‡ II	20	1.7		2.34		N.S.*		2.2	
Ratio, hydrochlorothiazide-prednisone to control	II	5	2.7		5.12		N.S.*		4.7	

N.S.* Not significant due to use of supplemental potassium
† Decrease
‡ Due to chloride loading

another group of 15 patients with congestive heart failure. These patients were followed over a 7- to 10-day interval while receiving only bed rest, low salt and digitalis. In the present study weight losses of less than one-quarter pound per day during the stabilization period were observed in 8 patients, 5 of whom were cirrhotics. In our experience, and that of others (Carbone and Matthews[4]), simple bed rest and salt restriction rarely improve the immediate excretion of excess salt and water in patients with cirrhosis complicated by ascites.

With hydrochlorothiazide a disproportionate increase occurred in both sodium and chloride excretion compared with the increase in urinary volume. This is in agreement with previous reports on the trial of this new diuretic in edema cases (Hejtmancik, Herrmann and Kroetz[15], Keller[16], Losse *et al.*[19], Esch, Wilson and Freis[11]). Despite the poor response to hydrochlorothiazide in our patients with "refractory edema" due to cirrhosis or nephrosis, the average increase in urinary responses, when compared with the pretreatment values, were considerable (Tables 4 and 6).

The data in Tables 4 and 6 suggest that addition of prednisone did little to improve the urinary output of sodium but did produce a significant "free water" diuresis. When the responses of the 5 patients given prednisone-hydrochlorothiazide are compared with their own control data rather than with Group II as a whole, the results are more impressive (Tables 3 and 5). The dramatic natruretic response seen when meralluride was administered with hydrochlorothiazide would suggest that more than an additive effect (Pitts[26]) was present.

Results of chloride loading and meralluride injection were included in order to compare the relative efficacy of these forms of therapy with hydrochlorothiazide. Alternate day treatment with acetazolamide and hydrochlorothiazide was tried because of a previous report recommending this procedure (Laragh, Heinemann and Demartini[17]). However, this particular diuretic plan was discontinued early in the study because of the disappointing sodium excretion observed.

The average net increase in urinary potassium was less than 50% in excess of the "control" level (Tables 4 and 6). Although the urinary potassium was less than that of either sodium or chloride, it should be noted that some excretion of this electrolyte does occur. This should be taken into account whenever prolonged hydrochlorothiazide therapy is undertaken.

Acetazolamide was found to be effective in reducing the serum bicarbonate elevation in 3 patients where such had occurred during the latter phase of hydrochlorothiazide administration. Serum bicarbonate elevation following hydrochlorothiazide treatment has been reported by Losse *et al.*[19] and by ourselves (Porter and David[29]) in patients receiving hydroflumethiazide. This effect may be due to the lower carbonic anhydrase inhibiting action of the dihydrogenated compounds compared to chlorothiazide. This activity would encourage the excretion of chloride to the exclusion of bicarbonate and, in turn, would produce the serum electrolyte pattern of hypochloremic alkalosis.

Our results agree with the previous reports of others on the effectiveness of hydrochlorothiazide in salt retention associated with congestive heart failure (Cassano *et al.*[5], Hejtmancik, Herrmann and Kroetz[15], Platts[28], Brest and Likoff[2], Nicolay[25], Keller[16]). They appear less dramatic since the method of study we used provides greater than normally expected control levels for

† Due to chloride loading

comparison. However, when comparison is made with the responses obtained for the third day of the control period (Table 6), closer agreement with the results reported by others is seen.

With respect to the use of corticosteroids with diuretics, several workers have used steroids in combination with either chlorothiazide or meralluride (Nicolay[25], Carbone and Matthews[4], Morrison and Chalmers[24], Redeker, Kuzma and Reynolds[32], Magid and Forsham[21]). As shown in Figs. 2 and 3 and pointed out previously (Carbone and Matthews[4], Redeker, Kuzma and Reynolds[32]), cessation of steroid results in immediate return of diuretic refractoriness. In the present study no infections secondary to steroid therapy were encountered, nor were any of the other side effects common to the use of high doses of exogenous steroid observed. This may be due to the fact that none of our patients were treated for prolonged periods. However, Redeker, Kuzma and Reynolds[32] used 6-methyl prednisolone and chlorothiazide for long periods of time without complications in treating cirrhotics. Also, we were able to rapidly withdraw steroids in patients treated less than 10 days without observing any adverse reactions.

The exact mechanism by which prednisone enhances the diuretic effect of the benzothiadiazides in cirrhosis is unknown (Carbone and Matthews[4], Redeker, Kuzma and Reynolds[32]). One possibility is that prednisone inhibits aldosterone action on the kidney. In cirrhosis of the liver, increased aldosterone secretion occurs (Dyrenfurth *et al.*[10], Chart and Shipley[7], and Wolff, Koczorek and Buchborn[39]). Aldosterone exerts a sodium-retaining effect on the kidney (Prunty *et al.*[30], Thorn[36], and Salassa *et al.*[35]) and, more specifically, on the renal tubule (Welt[37]). A number of workers have produced profuse diuresis and natruresis by blocking aldosterone with steroids in cirrhotic patients (Coppage *et al.*[8], Wolff, Koczorek and Buchborn[39], and Cejka, deVries and Borst[6]). Dingman *et al.*[9] favor this mechanism and further suggest that the free water diuresis from use of hydrocortisone or prednisone might be explained through neurohypophyseal inhibition of antidiuretic hormone secretion. Raisz *et al.*[31] administered hydrocortisone to patients with increased aldosterone levels resulting from salt restriction. They suggested that the water diuresis was probably due to altered renal tubular permeability to water, or to a redistribution of solute resorption between proximal and distal tubules.

Another explanation for the natruretic effect of prednisone relates to the "glomerular-tubular" imbalance present in edematous states (Pitts[26]). Burnett[3], and Levitt and Bader[18] have called attention to a renal effect of exogenous adrenal steroid which increases the filtered load of sodium. This might account for the ability of prednisone to potentiate benzothiadiazide blockage of sodium resorption (Ford[12], Hejtmancik, Herrmann and Kroetz[15], Mertz and Schettler[23], Ford[13], Pitts *et al.*[27]) in states characterized by a preponderant tubular reabsorption phase (Pitts[26]).

From our results we feel that the use of combined steroid-diuretic therapy is best reserved for those patients who are unresponsive to conventional forms of treatment. Also, in the present state of knowledge, such therapy is best undertaken in a hospitalized patient where constant observation is possible. Although the results in the 5 patients so treated were not as dramatic as had been hoped for originally, 3 of the 5 showed distinct improvement during the period of therapy.

Summary. Hydrochlorothiazide was used as a diuretic in 20 hospitalized patients, 11 of whom had congestive heart failure, 8 cirrhosis and 1 nephrosis. All patients were subjected to an initial 3-day "control" stabilization period in order to offset the influence of such variables as bed rest, digitalization and salt-free diet on their subsequent response to diuretics. Daily measurements of body weight, blood pressure and urinary volume and electrolyte excretions were made. Serum electrolytes and bicarbonate were measured daily during the initial 3-day "control" period and twice weekly during the therapy period. Blood urea nitrogen determinations were made weekly. Patients were started on 50 mg. of hydrochlorothiazide orally, given three times daily after meals. Of the 11 patients with congestive heart failure, one was started on this dosage plus an additional 75 mg. given at bed time while another was given this additional amount on the eighth day of trial. Duration of hydrochlorothiazide administration averaged 13.5 days (range 5 to 40 days). Evaluation of diuretic response was based on changes in the body weight and urinary sodium excretion. In the patients with congestive heart failure, the response to hydrochlorothiazide was excellent in 5, good in 4, and fair in 2. Four of the cirrhotic patients and the 1 nephrotic patient failed to respond satisfactorily to initial use of hydrochlorothiazide. Consequently, other diuretics were added in an attempt to adequately treat these patients. With the concomitant use of hydrochlorothiazide and prednisone, 3 of these 5 patients responded satisfactorily. The remaining 2 proved refractory to the other forms of therapy such as combinations of hydrochlorothiazide and meralluride, meralluride and "chloride loading" and alternating daily therapy with hydrochlorothiazide or acetazolamide. The two cirrhotic patients with ascites are presented as case reports with charts showing the urinary responses and changes in the serum electrolytes for each procedure tried. Our results suggest that combined steroid-diuretic therapy is best reserved for those patients who are unresponsive to conventional forms of treatment. On the other hand, when allowance is made for the study method we used, that is, employment of an initial 3-day stabilization period, the results we obtained with hydrochlorothiazide in patients with congestive heart failure compare very favorably with other workers' results as to the efficacy of this new diuretic agent.

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SUMMARIO IN INTERLINGUA

Hydrochlorothiazida Usate Sol in Congestive Disfallimento Cardiac e in Combination con Prednisona e Altere Diureticos in Cirrhosis e in Nephrosis

Hydrochlorothiazida esseva usate como diuretico in 20 patientes hospitalisate, incluse 11 con congestive disfallimento cardiac, 8 con cirrhosis, e 1 con nephrosis. Omne le patientes esseva subjicite initialmente a un periodo stabilisatori de "controlo" de un duration de tres dies con le objectivo de neutralisar le influentia de variabiles como allectamento, digitalisation, e dieta asalin super le subsequente responsa diuretic. Esseva effectuate mesurationes diurne del peso corporee, del tension de sanguine, del volumine de urina, e del excretion urinari de electrolytos. Le concentrationes seral del electrolytos e le bicarbonato del sero esseva mesurate diurnemente durante le tres dies del periodo initial de "controlo" e duo vices per septimana durante le periodo del therapia. Determinationes del nitrogeno de urea sanguinee esseva effectuate septimanalmente. Le patientes recipeva initialmente 50 mg de hydrochlorothiazida per via oral, tres vices per die post le repasto. Inter le 11 patientes con congestive disfallimento cardiac,

(Continued on page 532)

POTENTIAL HARMFUL EFFECTS OF TREATING PULMONARY ENCEPHALOPATHY WITH A CARBON DIOXIDE BUFFERING AGENT*

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Tris (hydroxymethyl) aminomethane is an organic buffering agent which combines with carbonic acid to form a bicarbonate complex, thereby lowering blood CO_2 tension and raising blood pH. Nahas[3] maintained oxygenation in completely paralyzed dogs by insufflating 100% oxygen through the trachea (diffusion respiration). The animals were unable to eliminate CO_2 and developed severe respiratory acidosis. By infusing Tris Buffer, Nahas was able to maintain near normal blood pH, and the treated animals recovered quickly when mechanical respiration was provided; artificial respiration failed to revive animals not treated with the buffer. The improved tolerance to CO_2 accumulation was attributed to maintaining a near-normal blood pH, although the data indicated that the buffer also strikingly reduced the blood CO_2 tension. Since elevated CO_2 tension is more neurotoxic than depressed blood pH (Swanson, Stavney and Plum[4]), it appeared that the beneficial effects of Tris most likely resulted from binding dissolved blood CO_2. Whether, due to raising pH, or lowering $PaCO_2$, Nahas' experiments did suggest that Tris would be potentially useful to treat the encephalopathy accompanying CO_2 retention in man.

Before using Tris to treat severely ill patients with pulmonary encephalopathy, its effects were studied briefly on 3 patients with compensated CO_2 retention. When Tris was infused rapidly, alarming blood gas changes were induced.

Methods. Three patients were studied. Respiratory minute volume was measured with a Tissot balanced spirometer. Fifteen to 20 minutes were allowed for subjects to establish a baseline minute volume, following which the calculated minute volume was averaged from separate 5 to 7 minute observation periods. Heparinized blood samples were obtained from an indwelling femoral arterial needle. Arterial blood pH was determined with a Cambridge Research Model pH Meter outfitted with a Coleman glass electrode immersed at 37° C. in a constant temperature bath. Oxygen content and capacity and CO_2 content were determined by the technique of Van Slyke and Neill. Arterial blood CO_2 tension ($PaCO_2$) and serum bicarbonate ($^-HCO_3$) were derived from the Singer-Hastings nomogram. In one patient the electroencephalogram was monitored on an 8-channel electroencephalograph using needle electrodes with bipolar linkages. A 0.33M solution of Tris(hydroxymethyl)aminomethane‡ in saline was intravenously infused through an 18 gauge needle. The infusion apparatus was arranged so that changing from 5% dextrose and water to Tris was undetected by the patient.

Case Reports. Case 1. A 58-year-old man who had suffered increasing respiratory insufficiency for 10 years was admitted to the King County Hospital, Seattle, for the third time in 7 months complaining of dyspnea and ankle edema. He had a blood pressure of 140/80, a pulse of 72 and a respiratory rate of 24. The A-P chest diameter was increased.

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†John and Mary R. Markle Scholar in Medical Science.

‡Tris Buffer was kindly supplied by Abbott Laboratories, North Chicago, Illinois.

Expiration was prolonged. The liver was enlarged and he had ankle edema. His skin and mucous membranes were cyanotic. A chest roentgenogram demonstrated increased pulmonary radiolucency with blebs at both apices. The hematocrit was 54%, serum bicarbonate 36 mEq. per L. and serum chloride 79 mEq. per L. Initial treatment with mercurial diuretics, intermittent positive pressure breathing and O_2 in low concentrations improved the dyspnea and eliminated the ankle edema. On the 4th hospital day the effect of Tris was tested.

CASE 2. A 70-year-old man was admitted to King County Hospital complaining that for a year he had had increasing dyspnea. His blood pressure was 160/90, pulse 140, respiration 40 and temperature 98.2. He had pulmonary osteoarthropathy and an increased A-P chest diameter. Prolonged expiration with wheezing was noted and there were rales at both lung bases. The heart was enlarged to the anterior axillary line. A chest roentgenogram initially demonstrated cardiac enlargement and pulmonary engorgement, which cleared progressively during hospitalization. An electrocardiogram revealed A-V dissociation with nodal tachycardia, which later reverted to a normal sinus rhythm. The hematocrit on admission was 49.5%, the serum bicarbonate was 38 mEq. per L., serum sodium was 141.4 mEq. per L. and serum potassium was 5.2 mEq. per L. Initial treatment, directed towards correcting his congestive failure by digitalization, was largely ineffective in relieving his symptoms, but he improved after receiving intermittent positive pressure breathing and bronchodilators. On the 12th hospital day his response to Tris was tested.

CASE 3. A 38-year-old woman with a history of asthma and progressive pulmonary insufficiency was admitted to another hospital after developing drowsiness and confusion which progressed to coma. Blood gas studies on admission there demonstrated an arterial pH of 7.2, a $PaCO_2$ of 80 mm. Hg and an O_2 saturation of 36.5%. Treatment with a tracheotomy, intermittent positive pressure breathing, bronchodilators, antibiotics and intravenous sodium bicarbonate reversed her neurologic signs and she became able to converse rationally and feed herself. Six days before her admission to the University Hospital she sustained a period of asphyxia when her tracheotomy became occluded. Subsequent to this episode her mental status deteriorated.

On admission to the University of Washington Hospital, she was unable to respond to questions. Her eyes were open, and conjugately deviated to the right. She had a blink response to threat, and occasionally protruded her tongue on command. Her blood pressure was 120/85, pulse 100, and respiratory rate was 16. Motor cranial nerve function was intact. There was prominent snouting and an increased jaw jerk. Muscle tonus and stretch reflexes were increased in both arms. The stretch reflexes were difficult to obtain in the legs. There were bilateral extensor plantar responses. The extended wrists occasionally showed brief twitches suggesting a flapping tremor. There were coarse rhonchi and respiratory wheezes throughout both lungs. On the second hospital day her response to Tris was tested under electroencephalographic control.

Results. The blood gas findings and ventilatory measurements during Tris infusion are summarized in Table 1.

The first patient (Fig. 1) had a resting minute ventilation of 8.12 L. per min. The arterial blood pH was 7.47, the $PaCO_2$ was 58.5 mm. Hg, blood bicarbonate was 41.5 mEq. per L., and arterial blood O_2 saturation was 85%. Tris was infused intravenously at a rate of 3 to 4 mEq. per min. An arterial blood sample taken when 45 mEq. of Tris had been infused had a pH of 7.61, a $PaCO_2$ of 48 mm. Hg, a bicarbonate of 49 mEq. per L. and an O_2 saturation of 70%. Respiration had decreased to 4.93 L. per min. Further measurement of respiration was impossible because of intolerance of the mouth piece and nose clamp. After a total of 90 mEq. of Tris had been given, the arterial pH was 7.65, the $PaCO_2$ was 50 mm. of Hg, the bicarbonate was 54 mEq. per L. The arterial oxygen saturation had fallen to 46.2%. The patient had no symptoms from the infusion and his state of consciousness did not change.

The second patient had a resting minute ventilation of 11.2 L. per min. The arterial blood pH was 7.50, the $PaCO_2$ was 45.0 mm. Hg, the bicarbonate was 34.5 mEq. per L. and the O_2 saturation was 91.6%. Tris was infused at a rate of 3 to 4 mEq. per min. When 30 mEq. of Tris had been

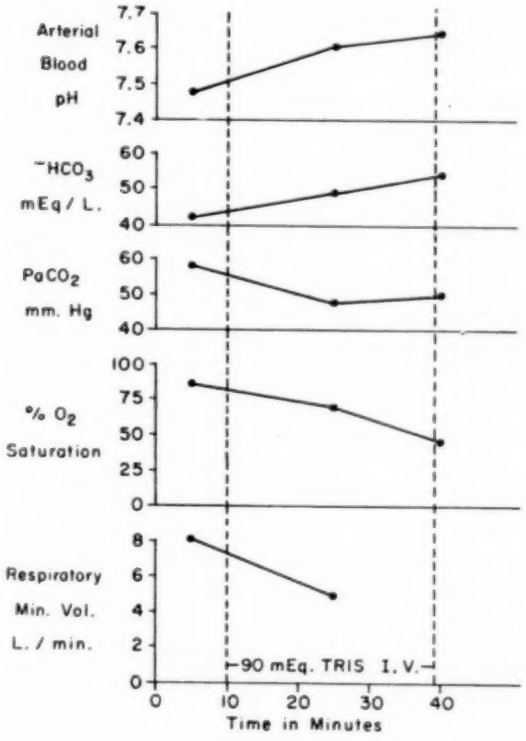

Fig. 1.

TABLE 1.

		Resp. Min. Vol. L./min.	*pH*	*$PaCO_2$ mm. Hg*	*HCO_3 mEq./L.*	*O_2% Sat.*
Case 1	Before Tris	8.12	7.47	38	41.5	85
	45 mEq. Tris	4.93	7.61	48	49	70
	90 mEq. Tris	—	7.65	50	54	46.2
Case 2	Before Tris	11.2	7.50	45	34.5	91
	30 mEq. Tris	8.5	7.55	44	38.0	86.1
	60 mEq. Tris	6.4	7.55	44	38.0	83
	8 min. after Tris	8.8	—	—	—	—
Case 3	Before Tris	—	7.37	49	45	55.4
	40 mEq. Tris	—	7.61	44	44	36.7
	20 min. after 50 mEq. Tris	—	7.62	41	41	40.8
	20 min. on O_2	—	7.37	49	45	79.6

infused, the respiratory minute volume had fallen to 8.5 L. per min. The arterial pH was 7.55, the $PaCO_2$ was 44 mm. of Hg, blood bicarbonate was 38 mEq. per L. and the O_2 saturation was 86.1%. Tris was discontinued at a total of 60 mEq. Ventilation at that time was 6.4 L. per min. The arterial blood pH was 7.55, the $PaCO_2$ was 44 mm. Hg, bicarbonate was 38 mEq. per L., and the O_2 saturation was 83%. Eight minutes after discontinuing Tris, ventilation had increased to 8.8 L. per min. The patient had no symptoms nor change in mental status during Tris infusion. The electrocardiograms of both the first and second patient showed no change in mechanism throughout the infusion.

Minute ventilation was not measured in the third patient because of lack of cooperation. Control studies of arterial blood demonstrated a pH of 7.5, a $PaCO_2$ of 49 mm. Hg, a bicarbonate of 44.5 mEq. per L. and an O_2 saturation of 55.4%. The infusion of 40 mEq. of Tris at 3 to 4 mEq. per min. raised the arterial blood pH to 7.62 and decreased the $PaCO_2$ to 44.5 mm. Hg. Blood O_2 saturation fell to 36.7%. The rate of infusion was slowed and Tris was finally discontinued when a total of 52 mEq. had been infused over a 17 minute period. Twenty minutes later the arterial blood pH was 7.62, the $PaCO_2$ was 42 mm. Hg and the O_2 saturation was 40.8%. After 20 minutes of breathing 100% O_2, the arterial blood pH was 7.57, the $PaCO_2$ was 49.5 and the O_2 saturation was 79.6%. The electroencephalogram before Tris infusion showed a predominant 4 to 6 cps frequency pattern with brief periods of superimposed 8 to 10 cps activity and a 3 to 4 cps slow wave focus in the left parietal-occipital region. There were no major changes in frequency, but a decrease in voltage was noted during Tris infusion. Tremulousness and agitation appeared during the infusion and subsided when 100% O_2 inhalation was supplied.

Discussion. In these patients with compensated CO_2 retention, rapid intravenous Tris Buffer infusions reduced $PaCO_2$, elevated blood pH and produced profound hypoventilation. Minute ventilation decreased 40% in the 2 measured cases and all 3 suffered a significant fall in arterial oxygen saturation and, because of the alkalosis, an even more profound fall in arterial oxygen partial pressure. Luchsinger *et al.*[2] who observed a 30% decrease in minute ventilation when Tris was given to normal subjects, ascribed the hypoventilation to "metabolic" alkalosis. It seems more likely, however, that the ventilatory response was a consequence of lowered $PaCO_2$, for although Tris is alkaline, part of its metabolic effects is to raise blood pH by binding dissolved CO_2 and thus reducing $PaCO_2$. This creates respiratory alkalosis, not metabolic alkalosis. The effect of Tris closely resembles the hypoventilation which results from infusing sodium carbonate (Na_2CO_3), another basic salt which lowers $PaCO_2$ and raises blood pH. Hesser[1] demonstrated long ago that the mechanism whereby sodium carbonate lowers ventilation is by reducing $PaCO_2$, since sodium *bi*carbonate ($NaHCO_3$), (which raises $PaCO_2$) stimulates ventilation, despite elevating the blood pH. Current experimental studies in this laboratory demonstrate that lowering $PaCO_2$ with Tris improves the electroencephalographic abnormalities induced by breathing mixtures of CO_2 and air. The results are consistent with previous experiments (Swanson, Stavney and Plum[4]), which demonstrated when blood pH and $PaCO_2$ are rapidly and independently varied, the electroencephalogram reflects arterial CO_2 ten-

sion changes rather than changes in blood pH.

Although effective treatment of pulmonary encephalopathy requires lowering the $PaCO_2$, it is hardly desirable to do this by a method which simultaneously induces further anoxemia. We are presently determining whether oxygen therapy will prevent the anoxemia which follows Tris-induced hypoventilation or whether artificial ventilation is required. Meanwhile considerable caution appears indicated before using parenteral buffering agents which lower $PaCO_2$ to treat patients with CO_2 retention.

Summary. Initial trials of a new organic buffering agent, Tris(hydroxymethyl)aminomethane, to treat pulmonary encephalopathy, produced striking hypoventilation and increased anoxemia in 3 patients with compensated CO_2 retention. The hypoventilation was probably due to the combination of Tris with free CO_2 which resulted in decreased CO_2 tension and a lessened stimulus to breathing. The anoxemia was sufficient to be potentially harmful. Buffering agents which abruptly reduce arterial CO_2 tension must be used cautiously in patients with CO_2 retention.

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SUMMARIO IN INTERLINGUA

Effectos Potentialmente Nocive del Tractamento de Encephalopathia Pulmonar con un Tamponator de Bioxydo de Carbon

Le prime essayos con un nove agente organic de tamponage, tris(hydroxymethyl)aminomethano, in le tractamento de encephalopathia pulmonar produceva frappante hypoventilation e augmentate grados de anoxemia in tres patientes con compensate retention de CO_2. Le hypoventilation esseva probabilemente causate per le combination del agente con CO_2 libere, resultante in un reduction del tension de CO_2 e un plus debile stimulo del respiration. Le anoxemia esseva satis marcate pro esser considerate como potentialmente nocive. Agentes tamponante que effectua un abrupte reduction del tension arterial de CO_2 debe esser usate cautissimemente in patientes con retention de CO_2.

THE CONTINUOUS FLOW SEPARATION OF LEUKOCYTES FROM HUMAN BLOOD*

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AND

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The separation of large amounts of plasma, platelets or erythrocytes from blood by centrifugation is relatively simple (Tullis[4]). The separation of leukocytes under sterile conditions, however, by standard techniques of centrifugation, sedimentation or filtration is tedious, time-consuming and often results in considerable damage to the leukocytes (Tullis[5]). Viable leukocytes may be rapidly separated under sterile conditions from plasma, erythrocytes and platelets by differential centrifugation in the Blood Fractionator† devised by Cohn and Tullis[6].

Many factors may influence the composition of the separated leukocyte preparations obtained from the Fractionator, for example, anticoagulant, temperature, centrifugal force, rapidity of separation, foaming and the unknown components of blood (Tullis *et al.*[6]). This report deals with the performance of the Fractionator in the separation of leukocytes from whole blood and the development of a method for the continuous and selective removal of leukocytes from the circulation of man under sterile conditions.

Methods and Equipment. The construction and operation of the ADL-Cohn Fractionator has been fully described by Tullis *et al.*[6]. The most satisfactory performance for leukocyte and platelet separation was obtained with the rbc-plasma bowl which was employed exclusively in these studies.

The rotational speed of the Fractionator was varied from 1,600 to 6,000 RPM which produced a centrifugal force of 30 to 1,200 times gravity at the opening leading from the bowl. For these studies 5,000 RPM was selected as most suitable for leukocyte separation. The rate of flow of blood into the separating bowl was varied from 50 to 120 ml. per minute. All separations were collected into sterile, siliconized bottles. The flow of plasma was diverted to another bottle after approximately 200 ml. of plasma was collected or a pink turbidity appeared. The leukocyte and platelet fractions were collected together with minimal erythrocyte contamination as judged by color. The red cell mass was collected separately in a third bottle.

Samples for determination of the white cell, platelet number and red cell contents were taken from each donor bottle and from the three collection bottles. Erythrocyte volume was measured by the microhematocrit method (McGovern, Jones and Steinberg[2]). Leukocytes were counted by the confirming double chamber method previously described (Bierman *et al.*[1]). Platelets were counted by the direct method (Tocantins[3]). National Bureau of Standards certified hemocytometers and automatic capillary filling Trenner pipettes were employed throughout.

Leukocytes and platelets were separated from 831 units of freshly drawn whole venous blood which had been collected in siliconized vacuum bottles with ACD solution, 4% sodium citrate or heparin as the anticoagulant (Group I). For comparison an additional 351 bowls were processed in 46 studies on 24 patients with malignant diseases other than leukemia and 127 bowls were processed in 15 studies

*Supported in part by Grant C-2272, National Cancer Institute, Bethesda, Maryland, and the Leukemia Research, Inc., Los Angeles, California.

†Cohn Blood Fractionator manufactured by Arthur D. Little, Inc., Cambridge, Mass.

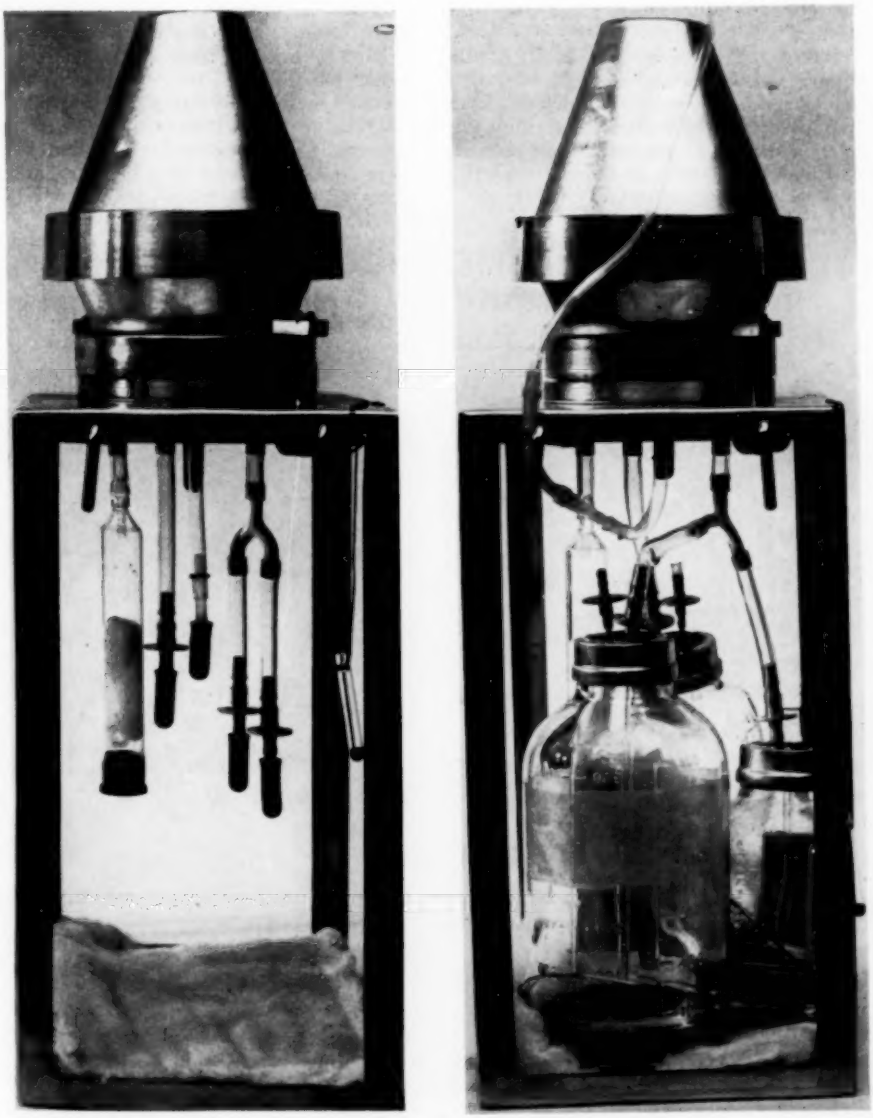

Fig. 1.—*A*. The bowl has been autoclaved and can be stored. Note the air filter packed with glass wool to allow for air exchange during and after autoclaving. *B*. Sterile siliconized collecting bottles attached. Note the Y tube at the right of the collecting outlets. Clamping of one side at the appropriate time allows collection of C.P. and a change of bottles whenever indicated. The siliconized non-wettable tubing leading upwards from the bowl conducts the blood from the donor bottle or from the patient to the bowl.

on 10 patients with leukemia during which arterial blood was led directly to the spinning bowl (Group II). The separations were performed at 15° to 23° C.

STERILITY. The separation bowl of the Fractionator revolves above a stationary base which contains the outlets to the collection bottles. Between the rotating and stationary parts is a carbon ring which when properly seated and mated with a stainless steel ring allows operation under sterile conditions. To collect and recombine the plasma and red blood cell fractions rapidly and return the desired quantities to the patient, required flexibility in the attachments of the outlets to the collecting bottles which complicated attempts to handle the entire separation unit and collection bottles in a sterile field. After many trials, this problem was solved by autoclaving the entire assembled separation unit (Fig. 1). Maintaining routine aseptic precautions, it was found that the outside of the bowl could then be handled freely without contamination of the internal surface or contents. Connections from the outlets to the bottles were capped until inserted into the sterile collection bottles.

GROUP I. SEPARATION OF VENOUS BLOOD FROM DONOR BOTTLES. Fresh whole blood from 831 normal donors was collected at room temperature into sterile siliconized vacuum bottles containing 125 ml. of ACD solution or 4% sodium citrate, or 25 mg. heparin as the anticoagulant. All tubing surfaces in contact with the blood were nonwettable or rendered so by silicone. The erythrocyte hematocrits averaged 42% with a range of 24 to 65%. The leukocyte concentration averaged 5,400 per c.mm. with a range of 1,800 to 12,900 per c.mm.

GROUP II. SEPARATION OF ARTERIAL OR VENOUS BLOOD DRAWN DIRECTLY INTO THE FRACTIONATOR. For the continuous flow studies the blood was drawn via an indwelling 16 gauge needle placed in a femoral artery and led to the fractionator by nonwettable tubing through a filter of 100 mesh siliconized nylon. A solution of saline containing 1.0 mg. heparin per ml. was introduced into the flowing arterial stream imme-

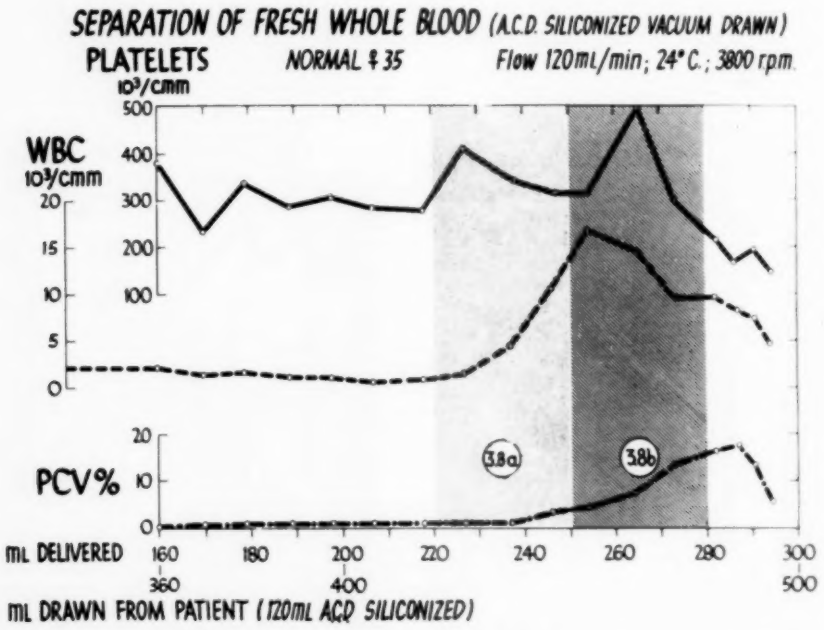

Fig. 2.—Consecutive samples from the plasma outlet port during separation at 3,800 rpm. 24° and blood flow of 122 ml. per min. Note that few leukocytes were not found until 220 ml. has been delievered. At this point a color change can be detected and C.P. collection begins, the first half designated as 3.8a, the last half 3.8b, as shown by the shading and insert numbers.

diately after leaving the patient. The flow of the heparinized saline was adjusted so that approximately 1.0 mg. heparin was mixed with 15 ml. of blood. Since a major portion of this blood was returned to the patient the amount of heparin used was decreased as the patient became heparinized. The total elapsed time for the blood to traverse the system from the patient to the bowl varied from 2 to 6 seconds. When indicated, the red cell mass was diverted into the plasma portion so that "reconstitution" of the blood could be rapidly performed and returned to the patient. Total elapsed time from beginning of flow of blood to bowl until beginning of return of "reconstituted" blood to patient varied from 6 to 15 minutes. The leukocyte and platelet components (buffy coat or cellular preparation) were available 4 to 10 minutes after blood began to flow to the bowl. The quantities of formed elements in the blood delivered to each bowl were calculated from samples of the inflowing arterial blood at the beginning and finish of each bowl taken before dilution with heparin.

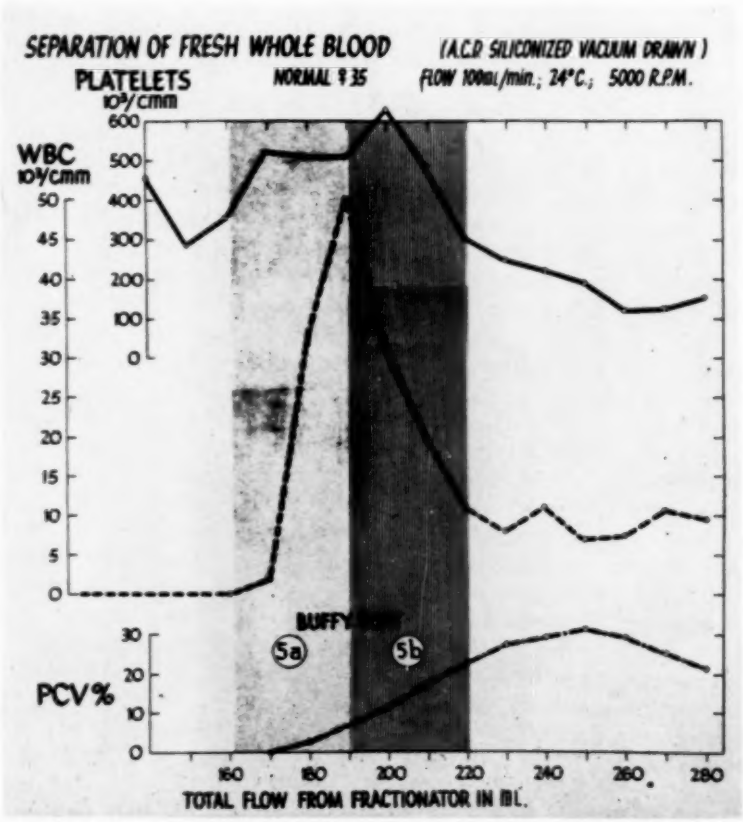

Fig. 3.—Separation of fresh whole blood of 100 ml. per min. at 5,000 rpm. Separation from 160 to 190 ml. designated as "*a*" contains predominantly lymphocytes and "*b*" at 190 to 220 ml. contains predominantly granulocytes, and a higher platelet and red cell content than "A." The numeral designates the RPM.

Results. To determine the optimal period for collection of the leukocytes, consecutive samples were collected from the plasma outlet during the separation of 12 units at varying revolutions per minute and centrifugal forces.

The appearance time of leukocytes

and platelets at the outlet varied with the RPM (centrifugal force) and the packed red cell volume (Figs. 2, 3, 4).

At 5,000 RPM (428 G's at the collecting port) leukocytes began to appear shortly before 450 ml. of normal blood had been delivered to the bowl and approximately 150 ml. of plasma had appeared in the collecting bottle (Fig. 1). The major portion of the leukocytes was contained in the subsequent 25 to 100 ml. Over 500 separations at 5,000 RPM revealed a wide range in leukocyte concentration in the plasma, cellular preparation (C.P.) and erythrocyte portions. The leukocyte concentration in the cellular preparation averaged 11,230 per c.mm. Differential counts showed the leukocytes in the "a" fraction (Fig. 2, 3, 4) to be predominantly lymphocytes. Those in the "b" fraction were predominantly granulocytes. Both fractions, however, contained lymphocytes and granulocytes. The "a" fractions contained from a trace to 49% erythrocytes averaging 14%. The "b" fraction ranged in content of red blood cells from 4 to 72% averaging 30%. When not separated into "a" and "b" portions the

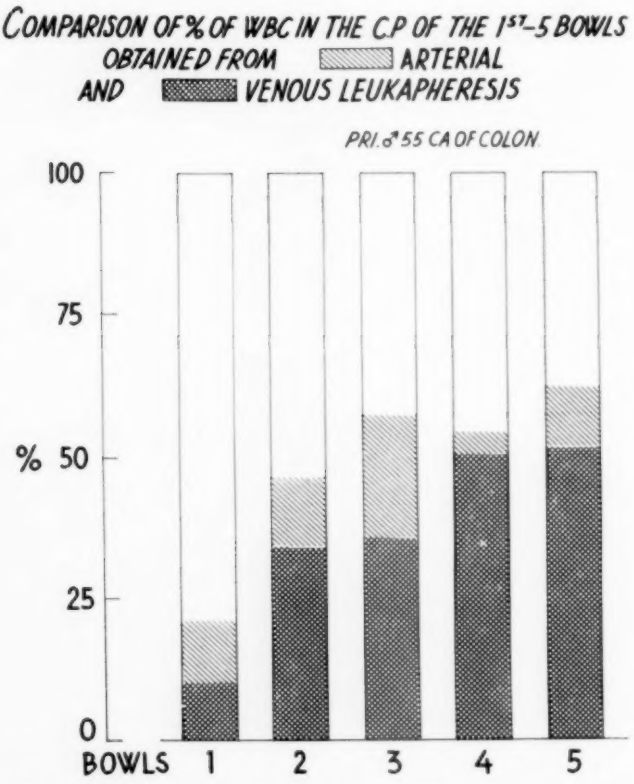

Fig. 4.—The white cell levels were within their comparable ranges in both studies. The first 5 bowls were comparable in times, flow and volumes separated. Temperatures were the same for both studies. The variation in per cent yield from bowl to bowl was in part related to the level of the leukocytes during the procedures.

erythrocyte content of the C.P. varied from a trace to 85% averaging 21% at 5,000 RPM. The platelet concentration in the cellular preparation varied from 20,000 to 1,260,000 per c.mm. averaging 285,000 per c.mm. In the "a" fraction at 5,000 RPM the platelet level varied from 5,000 to 1,670,000 per c.mm. averaging 200,000 per c.mm.

At 5,000 RPM the plasma varied in platelet concentration from 0 to 950,000 per c.mm. averaging 140,000 per c.mm. More platelets were found in the plasma of units separated at speeds of 3,800 RPM or less than at speeds above this rate. At 3,800 RPM, platelet distribution was approximately even throughout the different fractions (Fig. 2) and the total extraction of platelets in the plasma fraction was relatively free from leukocyte and erythrocyte contamination and can be further concentrated as described by Tullis *et al.*[6].

The erythrocyte mass derived from separation at flow rates of approximately 50 ml. per minute and 5,000 RPM varied in packed red cell content from 33 to 97%, averaging 77%. The leukocyte concentration of the red blood cell mass of normal venous blood varied from 400 to 9,000 per c.mm., averaging 3,800 per c.mm. Platelet levels in the erythrocyte mass varied from 500 to 600,000, averaging 67,000 per c.mm.

Various attempts to improve the percent of yield of leukocytes by varying the RPM during fractionation were not uniformly successful. For example, slowing the RPM at the end of the run and allowing more cellular preparation to drain, recycling the plasma or adding saline during this period, or decreasing the rate of flow of blood for the last 25 to 50 ml. did not consistently increase the yields.

At the lower speed of 3,800 RPM less packing of red cells was obtained and more plasma remained trapped in the mass. Conversely slower flow rates with proportionally longer exposure to centrifugal force decreased trapping of plasma in the red blood cell mass.

Decreasing flow rates which thereby increased the time the leukocytes were exposed to centrifugal force likewise did not consistently improve the yields nor decrease contamination with red cells. Addition of dextran, dextrose, and so forth, did not significantly increase the yield of leukocytes.

There was no correlation between percent of leukocytes collected and the time interval between donation and separation when this was less than 4 hours; yields were generally less, however, when this period exceeded 4 hours.

Hemolysis was not found when the blood was donated less than 4 hours before fractionation and had not been chilled. In blood donated more than 24 hours before separation and chilled to the usual banking temperatures, hemolysis of slight to moderate degree was occasionally observed. Chilling of freshly drawn blood in 10 separations did not appreciably improve the yield of leukocytes.

The yield of leukocytes and platelets from whole blood appears to be proportional to their concentration in the donor blood. In 214 units with complete counts on all portions the yield of leukocytes in the cellular preparation averaged 39% ± 14% with total recovery of 80% ± 20% (Table 1).

In the studies (Group II) wherein the blood flowed directly to the bowl from the patient the same variations existed as in the separation of single units of blood (Fig. 4). The conditions of operation such as temperature, RPM and anticoagulant were as nearly constant as possible for each patient yet variability of yield was still present. In the earlier studies rates of blood flow were slow (15 to 130 ml. per

min.) and varied during each study. However, later when more experience was gained, flow rates were constant for periods up to 2 hours and the variation of yield still persisted (Fig. 4) with the average percentage of white cells recovered being 56% ± 20% in the cellular preparation and a total recovery of 82 ± 21% (Table 1). Separation of arterial blood compared with venous blood from the same patient demonstrated a wide variation of yield (Fig. 4). The separation of arterial blood exhibited greater recovery of leukocytes in the cellular preparation than from the venous blood. In non-leukemic patients, arterial blood separation gave an average recovery of 56% of the leukocytes in the C.P. whereas with venous blood only 38% of the leukocytes were recovered, not significantly different from the normal donor recovery of 39%. The number of leukocytes recovered from the arterial blood was 17% greater than from venous blood, a difference greater than 11 times the standard error of the means 1.46 (Table 1).

TABLE 1.—LEUKOCYTE SEPARATION AT 5,000 RPM AT 20 TO 22°C.

	Venous blood from bottle	*Arterial blood flowing directly into Bowls*	
Clinical Status	*Normal*	*Normal*	*Leukemic*
Anticoagulant	*A.C.D.*	*Heparin*	*Heparin*
Number of Bowls	*214*	*351*	*127*
Donor			
vol. in ml.	604 ± 38	780 ± 140	872 ± 94
WBC × 10^3	5.37 ± 1.81	9.6 ± 5.8	87.9 ± 65.5
Content × 10^9	3.24 ± 1.10	7.6 ± 5.0	77.2 ± 57.6
Plasma		26 Bowls	59 Bowls
vol. in ml.	210 ± 25	335 ± 126	319 ± 59
WBC × 10^3	0.74 ± 0.56	0.6 ± 0.5	10.3 ± 16
Content × 10^9	0.16 ± 0.18	0.2 ± 0.2	3.2 ± 4.5
RBC			
vol. in ml.	282 ± 29.1	350 ± 130	300 ± 30
WBC × 10^3	4.0 ± 1.9	4.1 ± 3.8	22.5 ± 35.3
Content × 10^9	1.12 ± 0.59	1.6 ± 1.5	6.6 ± 9.6
Cell Preparations			
vol. in ml.	111.7 ± 10.5	133 ± 52	240 ± 76
WBC × 10^3	11.23 ± 4.89	31.9 ± 18.9	231.4 ± 171.6
Content × 10^9	1.25 ± 0.46	4.2 ± 2.6	53.0 ± 47.6
Reconstituted		325 Bowls	68 Bowls
vol. in ml.	—	555 ± 45	500 ± 110
WBC × 10^3	—	3.5 ± 3.5	5.8 ± 3.7
Content × 10^9	—	2.0 ± 2.0	2.9 ± 1.96
Leukocyte Recovery			
Total × 10^9	2.53 ± 0.68	6.2 ± 3.9	62.3 ± 45.2
% of Total	80 ± 20	82 ± 21	81.6 ± 26.4
% in C.P.	39 ± 14	56 ± 20	73.7 ± 27.4

When net leukocyte removal was calculated during continuous leukocyte withdrawal (leukapheresis) the loss of leukocytes in the unreturned plasma, in the tubing, filters and equipment and losses due to foaming and fragility were included. During leukapheresis of patients with leukocyte levels within the normal range the "reconstituted blood" returned to

the patient contained approximately 20% of the leukocytes entering the fractionator. The net loss to the patient of leukocytes per ml. of blood withdrawn, separated and returned to the individual averaged 78.8%. The net loss varied according to the level of the leukocyte count at the time each ml. of blood was withdrawn and was considerably greater in the patients with leukocytosis. Consequently, in leukemic subjects, the recovery of leukocytes in the C.P. was increased when blood was withdrawn from patients with elevated leukocyte levels (Table 1).

The difference between the means of the per cent of recovery of leukocytes in the C.P. in the leukemic and the non-leukemic arterial blood was 18% greater than 6 times the standard error of means (2.68). The difference of the means of normal venous blood in individual donations and leukemic arterial blood was 35% greater than 13 times the standard error of the means (2.62). The percentage of *total* leukocyte recovery in all 3 groups is not significantly different.

Paper strip electrophoresis of the plasma and cellular preparations revealed no significant denaturation of proteins after separation.

Discussion. The preparation of pure leukocyte and platelet suspensions was not achieved by a single centrifugation since some red cell contamination existed due to intermingling of cell types with identical or overlapping specific gravities. It should be noted that although the number of leukocytes in the C.P. was approximately the same as that in the red blood cell mass in the normal donor blood (Table 1) the volume of the C.P. was almost 1/3 that of the red blood cell mass.

The reduction of volume of the C.P. from that of the whole blood permits further separation and purification for biochemical and other analyses of the leukocytes and platelets in a fresh state by more refined techniques of sedimentation, flotation, and centrifugation. Occasionally a bowl will not produce the anticipated separation despite all precautions. This in part is responsible for the considerable range of the composition of the C.P. and possibly related to factors of leukocyte behavior and constituents yet unknown, such as serological types, cell "stickiness," and mechanical performance of the device.

The ability to obtain plasma, C.P., or red cell mass rapidly and under sterile conditions for reinfusion and transplantation is a decided advantage. For the purpose of leukapheresis, plasmapheresis and other similar studies, the Cohn Blood Fractionator can be safely utilized. It is anticipated that as experience is gained, the versatility of such separations will be expanded.

Summary. 1. The formed elements of human blood may be separated rapidly and continuously under sterile conditions in the ADL-Cohn Fractionator, ready for infusion or study in the fresh state with a minimum of manipulation and loss of time.

2. Operation of the fractionator at 5,000 RPM with blood inflow rates of 50 to 100 ml. per minute affords the most appropriate conditions for obtaining high content leukocyte material in a fresh state.

3. Chilling failed to improve the separation of leukocytes in these studies.

4. Better leukocyte separation was obtained with arterial blood than with venous blood.

5. Eighty per cent or more of the leukocytes presented to the fractionator can be continuously removed through leukapheresis.

ACKNOWLEDGMENT. The assistance of Dr. Russel T. Jordan in the studies on sterility is gratefully acknowledged. The authors also gratefully acknowledge the technical assistance of F. L. Cordes, H. M. Watson and D. I. Schloredt.

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SUMMARIO IN INTERLINGUA

Separation, a Fluxo Continue, de Leucocytos ab Sanguine Human

1. Le formate elementos de sanguine human pote esser separate rapide- e continuemente sub conditiones sterile in le fractionator de Cohn (Arthur D. Little), con un minimo de manipulation e perdita de tempore e resultante in productos que es preste al infusion o al studio in stato fresc.

2. Le actuation del fractionator a 5.000 rpm e un influxo de 50 a 100 ml per minuta provide le plus appropriate conditiones pro le obtention de un alte contento de leucocytos in stato fresc.

3. Frigidation non meliorava le separation de leucocytos in iste studios.

4. Le separation de leucocytos esseva melior in sanguine arterial que in sanguine venose.

5. Octanta pro cento o plus del leucocytos presentate al fractionator pote esser separate continuemente per leucopherese.

SUMMARIO IN INTERLINGUA

(See page 458 for original article)

Le Effecto de Cortisona e de Triamcinolona Super le Terreno Immunologic e le Curso de Glomerulonephritis Experimental

Acetato de cortisona e triamcinolona deprime le formation de anticorpore anti sero de anate in conilios recipiente injectiones de nephrotoxic sero de anate anti ren de conilio. Le glomerulonephritis experimental productori de anticorpore specific, *i.e.* le anticorpore anti le fraction localisante del sero nephrotoxic es etiam deprimite, un facto que se face evidente in le transfusion de sero ab animales nephritic con e sin tractamento per acetato de cortisona e triamcinolona. Le transfusion de sero ab nontractate conilios nephritic resultava in immediate nephritis in sensibilisate animales, durante que le transfusion de sero ab conilios nephritic tractate con acetato de cortisona e triamcinolona produceva nulle morbo in sensibilisate animales. Glomerulonephritis experimental es meliorate in animales tractate con steroides non solmente per le depression del formation de anticorpore sed etiam per un directe effecto anti-inflammatori.

Triamcinolona ha circa 20 vices le efficacia de acetato de cortisona in le suprression de glomerulonephritis experimental. Uremia—que occurre regularmente in le non-tractate gruppo—occurreva in solmente 4 del 11 conilios tractate con acetato de cortisona e in solmente 2 de 20 animales recipiente adequate quantitates de triamcinolona.

BEHAVIOR OF HEPARINIZED ARTERIAL BLOOD ON HEMOSTASIS IN THE DOG HIND-LEG PREPARATION*

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AND

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The marked and durable hemostatic properties of citrated normal arterial blood, in contrast with the non-hemostatic citrated venous blood, were thoroughly described in previous papers[7,8].

The avoidance of blood coagulation by a mechanism other than calcium removal, that is, by heparin injection or by heparin added *in vitro* to blood, revealed a particular behavior of the hemostatic properties of arterial blood. Short durability of hemostatic properties in arterial blood samples, taken from heparin-resistant dogs (Cruz, Oliveira and Dietrich[5]) and recovery of hemostatic properties of arterial blood taken from heparin-labile dogs, after contact with some foreign surfaces, are presented in this paper.

Methods. Mongrel dogs taken from the animal city pound were used in all experiments. Hemostatic properties of blood samples were tested in the dog hind-leg preparation adapted for such studies (Cruz and Oliveira[7]). The heparin used was Liquemin from Roche (heparin solution of 5000 I.U. per ml.), and protamine sulfate (Roche) in a 1.0% solution. Normal and a few anemic hematological blood samples taken with Wintrobe oxalate mixture were used after previous determinations of hematocrit, hemoglobin, platelets, blood clot retraction time and coagulation time according to methods previously described (Cruz and Oliveira[7]). To analyze the results presented, one should recall that in dogs after injection of a standard dose of heparin (300 I.U. per kg.) the hemostasis of skin vessels varies individually in each animal (Cruz, Oliveira and Dietrich[5]): in 63% of the dogs hemostasis remains normal (5 to 12 minutes), in 18% it is prolonged (13 to 29 minutes) and in 19% it is disrupted (more than 30 minutes). In our studies, dogs with prolonged bleeding time were never used, only animals with normal bleeding time (heparin-resistant dogs) and with disrupted hemostasis (heparin-labile dogs).

Results. HEPARINIZED BLOOD IN CONTACT WITH UNCOATED GLASS. To interpret the resulting variations in this group we have to consider: a) behavior of each dog towards heparin; b) the manner of heparinization; and c) contact time. In Table 1 are shown the results, which may be summarized as follows:

Heparinization in vitro. When heparinized arterial blood is maintained in contact with glass for 30 or more minutes, irrespective of the heparin-resistance type of both donor and receptor dogs, it shows no hemostatic properties (10 determinations). When the time of glass contact is shorter (5 to 10 minutes) a difference is observed when the donor dog is heparin-resistant or heparin-labile, irrespective of the heparin-resistance of the receptor dog. In this case blood from heparin-resistant

*This study was aided by the Conselho Nacional de Pesquisas and by a grant from Dr. Guilherme Guinle.

TABLE 1.—HEMOSTATIC BEHAVIOR OF HEPARINIZED (100 TO 300 I.U./KG. OR 100 ML.) ARTERIAL BLOOD (DONOR DOG) COLLECTED UNDER PETROLEUM JELLY OR ALVEOLAR AIR, AFTER CONTACT WITH UNCOATED GLASS, ON THE HIND-LEG PREPARATION (RECEPTOR DOG).

Method of heparinization	*Heparin-resistance type*		*Contact time (min.)*	*Hematology*								*Number of determinations*	*Bleeding time (minutes)*		
				Hemoglobin (gm./100 ml.)		*Hematocrit (%)*		*Platelets (ml./100 ml.)*		*Coagulation (minutes)*		*Clot retraction (minutes)*			*Previous citrated arterial blood*	*Heparinized arterial blood*	*Posterior citrated arterial blood*
	Donor	*Receptor*		*Heparinization*		*Heparinization*		*Heparinization*		*Heparinization*		*Heparinization*					
				Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*				
In vitro	HR	HR or HL	5–20	7.1–13.3	8.2–11.0	23–48	26–38	0.12–0.38	0.28	2–4	4	2–5	2	11	6–9	6–10	6–9
			30 or more	7.1–11.3	8.2–11.0	23–38	26–38	0.12–0.38	0.28	2–3	4	1–3	2	7	6–8	+30	>15
	HL	HR or HL	5–10	3.4–12.5	—	15–45	—	0.05–0.65	—	2–4	—	2–4	—	5	6–9	+30	>15
			30 or more	10.9–12.0	—	42	—	—	—	—	—	—	—	3	6–8	+30	>15
In vivo	HR	HR or HL	5	6.8–13.0	—	23–32	—	0.14–0.34	—	2–3	—	2–7	—	17	5–8	4–8	6–8
			10 or more	6.8–13.0	—	23–32	—	0.15–0.34	—	2–3	—	2	—	10	6–8	+30	>15
	HL	HR	5	7.5–8.9	—	26–29	—	0.20–0.29	—	2–3	—	1–7	—	9	6–7	6–8	6–7
		HL	5	7.5	—	26	—	0.21	—	3	—	2	—	4	6–7	+30	>15
	HL	HR or HL	10 or more	7.5–12.5	—	26–45	—	0.20–0.34	—	2–4	—	4–9	—	6	6–8	+30	>15

HL = Heparin-labile dog

HR = Heparin-resistant dog

donors keeps its hemostatic capabilities even when contact is prolonged to 20 minutes (11 determinations), whereas blood from heparin-labile donors stays non-hemostatic (5 determinations). These blood samples behave *in vitro,* when contact is short, as they do in the circulation of the donors from whom the samples were taken, that is, they show no hemostatic properties when coming from a heparin-labile dog and retain these properties when obtained from a heparin-resistant dog.

Thus, there is no alteration of the hemostatic properties of heparinized blood when it is in contact with uncoated glass for less than 20 minutes. After longer periods of contact, all samples lose the ability to control bleeding.

Heparinization in vivo. When contact is prolonged for 10 or more minutes, irrespective of the heparin-resistance of donor or receptor dogs, blood samples always show no hemostatic properties (22 determinations). After very short contact time (5 minutes), blood from a heparin-resistant donor, irrespective of the receptor heparin-resistance, keeps its hemostatic properties (17 determinations). When blood is taken from a heparin-labile donor, however, its behavior in short time contact varies according to the heparin-resistance of the receptor dog. If the receptor is heparin-labile, the blood shows no hemostatic capacities (4 determinations), whereas if the blood is used in a hind-leg of a heparin-resistant dog it becomes hemostatic (9 determinations).

HEPARINIZED BLOOD IN CONTACT WITH SILICONED OR PARAFFINED GLASS. Entirely different results are obtained with silicone or paraffin coated surfaces than when in contact with glass. In this group, as shown in Table 2, the manner of heparinization is of no importance. Blood samples heparinized *in vitro* or *in vivo* behave similarly.

Contact period between 0 and 60 minutes. Heparin-resistant dog arterial blood samples keep their hemostatic capacities in these protected surfaces for a much longer period of time than when in contact with glass (up to 60 minutes instead of 20 minutes as with glass surface), as shown in 22 determinations. When blood arterial samples are taken from heparin-labile dogs, they reacquire hemostatic abilities when in contact with siliconed or paraffined surfaces, as long as this contact is not prolonged for more than one hour (11 determinations).

Contact period between 90 and 210 minutes. After this prolonged contact time, every arterial blood sample from heparin-resistant or heparin-labile dogs shows no hemostatic effect in the hind-leg preparation (16 determinations).

BEHAVIOR OF HEPARINIZED ARTERIAL BLOOD AFTER NEUTRALIZATION BY PROTAMINE. That heparinization of blood causes irreversible modifications is shown by the results of heparin neutralization with optimal amounts of protamine after previous addition of sodium citrate to prevent coagulation. Again differences were observed according to the foreign surface, the method of heparinization, and to the amount of time allowed for the heparinized blood to stay as such before neutralization with protamine.

Uncoated glass. When heparinization is carried out *in vitro,* the immediate neutralization by protamine, preceded by addition of citrate, is unable to retain the hemostatic properties of arterial blood (4 determinations). When blood is heparinized *in vivo* and protamine neutralization is performed *in vitro* immediately, if the donor is heparin-resistant, the samples keep the hemostatic power, in some cases, for at least one hour (7 determinations). If protamine neutralization is carried out after 5 minutes of contact, still normal results are obtainable (2 deter-

TABLE 2.—HEMOSTATIC BEHAVIOR OF HEPARINIZED (300 I.U./KG. OR 100 ML.) ARTERIAL BLOOD *IN VIVO* AND *IN VITRO* (DONOR DOG) COLLECTED UNDER PETROLEUM JELLY OR ALVEOLAR AIR, AFTER CONTACT WITH SILICONED AND PARAFINED GLASS, ON THE HIND-LEG PREPARATION (RECEPTOR DOG).

Heparin resistance type		*Contact time (min.)*	*Hematology*										*Number of determinations*	*Bleeding time (minutes)*		
			Hemoglobin gm./100 ml.		*Hematocrit (%)*		*Platelets ml./100 ml.*		*Coagulation (min.)*		*Clot retraction (min.)*			*Previous citrated arterial blood*	*Heparinized arterial blood*	*Posterior citrated arterial blood*
			Heparinization		*Heparinization*		*Heparinization*		*Heparinization*		*Heparinization*					
Donor	*Receptor*		*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*				
HR	HR or HL	5–60	5.7–12.0	5.8–12.7	17–46	19–50	0.10–0.68	0.10–0.64	3–4	3–6	1–2	2–9	22	6–7	7–8	6–8
HL	HR or HL	5–60	7.5–13.7	15.1	25–45	55	0.16–0.37	0.40	2–4	6	2–7	7	11	6–10	6–11	6–7
HR or HL	HR or HL	90–120	5.7–13.7	5.8–15.1	17–46	17–55	0.10–0.68	0.14–0.60	2–5	2–6	1–5	6–9	16	6–8	+30	>15

TABLE 3.—HEMOSTATIC BEHAVIOR OF HEPARINIZED (300 I.U./KG. OR 100 ML.) ARTERIAL BLOOD *IN VIVO* AND *IN VITRO* (DONOR DOG) COLLECTED UNDER PETROLEUM JELLY IN UNCOATED AND IN SILICONED GLASS, IMMEDIATELY CITRATED AND NEUTRALIZED WITH PROTAMINE *IN VITRO*, AND TESTED IN THE HIND-LEG PREPARATION (RECEPTOR DOG).

Surface of contact	Method of heparinization	Heparin resistance type		Time before neutralization by protamine (min.)	Hematology										Number of determinations	Bleeding time (minutes)		
					Contact time with foreign surface (min.)	Hemoglobin (gm./100 ml.)		Hematocrit (%)		Platelets (ml./100 ml.)		Coagulation (minutes)		Clot retraction (minutes)			Previous citrated arterial blood	Heparinized arterial blood	Posterior citrated arterial blood
		Donor	Receptor			Heparinization		Heparinization		Heparinization		Heparinization		Heparinization					
					*	Before	After	Before	After	Before	After	Before	After	Before	After				
Uncoated glass	*In vitro*	HR or HL	HR	immediately	0–60	9.3–12.0	3.4–9.6	34–42	15–33	0.34–0.42	0.27–0.38	4	2	5	8	4	6–7	+30	>15
		HR	HR or HL	immediately	0–60	5.1– 8.7	5.1– 8.0	20–30	20–31	0.15–0.41	0.04–0.40	3–5	4	1–3	1–14	7	6–7	6–8	6–7
			HR	5	5	5.1	5.0	20	19	0.41	0.41	5	3	3	3	2	6	6–8	6–7
				10	10	5.1	5.7	20	22	0.41	0.41	5	4	3	1	2	6–7	23–26	>15
				60	60	5.1–11.1	5.1– 7.7	20–29	20–28	0.34–0.41	0.10–0.40	5	4	3	1	3	6–7	+30	>15
Siliconed glass	*In vivo & in vitro*	HR	HR	0–60	0–60	7.6–12.0	6.7–12.0	27–46	22–50	0.10–0.68	0.15–0.64	3–4	3–5	1	1–2	7	6–7	6–10	6–7
				90	90	7.6–12.0	7.3–11.8	27–46	25–48	0.10–0.68	0.18–0.61	3–4	4	1	1	2	6–7	26–+30	>15

HR = Heparin resistant dog
HL = Heparin labile dog

*Time before the start of the hind-leg preparation. Zero time means that the blood stayed in contact with foreign surface only during time of hind-leg test.

minations); if done after 10 minutes of contact very prolonged bleeding times are observed (2 determinations); but if carried out after one hour of contact, the hemostatic properties disappeared completely (3 determinations), showing that early neutralization can prevent the loss of hemostatic abilities but cannot recover them if they are lost by prolonged contact with glass.

Siliconed glass. Protamine neutralization carried out even after one hour of contact of the heparinized blood with silicone still preserves the hemostatic properties of these samples (7 determinations). Nevertheless, if neutralization is carried out in a period in which the blood has already lost its hemostatic capabilities (90 minutes) then these properties are not recovered (2 determinations).

BEHAVIOR OF HEPARINIZED VENOUS BLOOD. To test the possible corrective effect of heparin in non-hemostatic venous blood, 3 determinations were carried out (one in glass, 2 in siliconed glass) with venous blood instead of arterial blood. The usual result with this type of blood was found, that is, a bleeding time longer than 30 minutes. There was also no hemostasis observed in 5 experiments in which nonrearterialized and heparinized venous blood stayed in contact with siliconed glass beads in a siliconed flask for more than one hour.

Discussion. COMPARATIVE ENDURANCE BEHAVIOR OF HEPARINIZED AND CITRATED BLOOD. To understand the significance of the results it is necessary to call attention to the fact that citrated arterial blood, even when in contact with glass, keeps its hemostatic properties for 6 or more hours (Cruz and Oliveira[7]). In contrast, heparinized arterial blood, taken from heparin-resistant dogs, seems very sensitive to foreign surfaces, especially uncoated glass.

HEMOSTASIS DISRUPTION OF HEPARIN-RESISTANT BLOOD. Thirty minutes of contact with glass is enough to convert hemostatic arterial blood heparinized *in vitro* to non-hemostatic blood, although shorter contact times are unable to carry out this conversion. The periods necessary to convert arterial heparin-resistant blood into non-hemostatic blood are even shorter when heparinization is carried out *in vivo*. This significant difference (10 minutes are enough for this conversion) once more shows how different are the biochemical combinations of heparin *in vitro* and *in vivo* (lipemia clearing activity being the first one described in this connection). In silicone or paraffin coated glass, the heparinized blood *in vitro* or *in vivo*, taken from a heparin-resistant donor, keeps its hemostatic power for much longer periods (60 minutes) than when in contact with glass. This demonstrates the importance of the type of foreign surface in the deterioration of the hemostatic abilities of heparinized blood.

In order to observe whether the effect of heparinization could be reversed by protamine neutralization after previous addition of citrate to prevent coagulation, various experiments were performed. These showed that, when protamine is added within the period during which the blood still retains its hemostatic properties when heparinized, this capacity is maintained. It thus acquires the endurance of true citrated blood (positive hemostatic effect after one hour contact with uncoated glass). However, if heparinized blood has already lost its hemostatic power when citrate and protamine are added to it, the blood then remains non-hemostatic, protamine being thus unable to reverse the disrupting hemostatic action of heparin.

HEMOSTATIC CONVERSION OF HEPARIN-LABILE BLOOD. Most unexpected have been the results with heparinized blood

taken from heparin-labile dogs. This non-hemostatic blood (since the bleeding time in these dogs after heparin injection is more than 30 minutes), as expected, remains non-hemostatic in contact with glass, regardless of the manner of heparinization. When in contact with siliconed or paraffined coated surfaces, however, this blood is converted into full hemostatic blood. It appears, therefore, that if some foreign surfaces adsorb or destroy a plasma constituent necessary for hemostasis (as shown by negative hemostatic effect after glass contact with blood taken from heparin-resistant dogs), some other surfaces could also adsorb or destroy an inhibitory component involved in the same phenomenon.

HEPARIN, PLASMA GLOBULIN AND FOREIGN SURFACE CONTACT. The results indicate that in addition to the antithrombin and antiprothrombin action of heparin in coagulation, this mucopolysaccharide has an antihemostatic activity. This is shown in the study of heparinized blood samples in the hemostasis of the hind-leg preparation observed by bleeding time determinations. The antihemostatic effect here described has been studied after the withdrawal of blood from the organism. Heparin seems to render some plasma components sensitive to contact with glass surface, since its intravenous injection into heparin-resistant dogs does not interfere with the hemostasis of small vessels, even though it may render the whole blood of the animal (Cruz, Oliveira and Dietrich[5]) incoagulable for many hours. Nevertheless, when heparinized blood leaves the endothelial walls, the type of surface with which it comes in contact has a somewhat deleterious effect on its hemostatic capacities, as shown by the results of this study.

Even after protamine neutralization, the effect of heparin on the plasma globulins, when blood contacts foreign surfaces, seems to be irreversible, since the hemostatic abilities of blood thus treated are lost, just like the blood samples not neutralized by protamine. The assumption of Fiescher[10] that, on account of the ready transfer of heparin from globulins to other substances (toluidin blue, protamine, and others), the union of heparin to globulin is more of a physicochemical nature than a true chemical union, this does not imply that globulins, that have been in loose contact with heparin, have the same characteristics they had before this contact.

As in lipemia clarification, a marked difference of *in vivo* and *in vitro* heparinization observed in hemostasis seems to indicate how intrinsically different are the connections of heparin with plasma components when inside or when outside the organism. *In vivo*, heparin seems to have preference for plasma components other than those involved in the mechanism of hemostasis, since protamine neutralization in these conditions keeps the blood hemostatic for much longer periods of time. *In vitro*, a condition that avoids the continuous organ supplementation of some plasma factor, heparin goes directly into union with hemostatic plasma components, thereby making the blood sample non-hemostatic in a very brief period.

After heparinization the sensitivity of blood to foreign surfaces is quite remarkable. This is in contrast to the long periods (6 or more hours) during which citrated arterial blood in contact with uncoated glass remains hemostatic at room temperature, when tested in the hind-leg preparation (Cruz and Oliveira[7]). Whether this lability of heparinized blood is connected with platelet behavior is not known. However, the maintenance of the platelet count and the behavior of these blood

samples, before and after heparinization, towards clot retraction, tend to stress that a plasma factor rather than the platelets is involved in the blood modifications occurring after foreign surface contact.

CORRELATION OF HEPARIN-FOREIGN SURFACE EFFECT WITH OTHER OBSERVATIONS ON HEMOSTASIS IN VIVO. These findings on heparin and hemostasis correlate quite well with some of our other observations on this subject. By plasma fractionation we were able to show plasma components with the property to convert non-hemostatic venous blood into hemostatic blood (Crug, Magalhaes and Oliveira[2]) and some other components able to convert the hemostatic arterial blood into non-hemostatic blood (Cruz, Magalhaes and Meis[3]). Both of these components have fractionation and electrophoretic properties (Magalhaes *et al.*[13]) of globulins, being probably connected with lipoproteins. Also the lipid moiety of lipoproteins, the phospholipid cephalin (phosphatydilethanolamine) has the ability to convert venous blood into hemostatic blood (Cruz, Magalhaes and Oliveira[4,9]).

HEPARIN EFFECT UPON PLASMA PROTEINS. Heparin, because of its high electronegativity, unites not only with coagulation factors but with various other plasma constituents. This broad spectrum of its reactivity with globulin obeys, nevertheless, a scale of priority in the union of heparin with plasma constituents, as shown in the work of Hoch and Chanutin[11]. These authors point out that heparin reacts in serum with some subfractions of beta globulin and alpha$_2$ globulin and then with albumin, in the order of decreasing affinity. This is confirmed by Nikkila[14] who adds that heparin has the strongest affinity for beta-lipoproteins, which is a contribution similar in concept to the work of Fiescher[10] and Chargaff[1] on other heparin-lipoprotein interactions. The electrophoretic mobility of the formed heparin-lipoprotein compound is proportional to the heparin concentration; the changes in the alpha$_2$ and alpha$_1$ globulin-albumin region of the Tiselius apparatus pattern in the higher heparin concentrations are, therefore, at least partly, due to the heparin-lipoprotein complex (Nikkila[14]). That heparin unites with some plasma component before being active was suspected from some of its effects. Lipemia clearing is only observed *in vivo* because heparin has to unite with a plasma factor (lipemia clearing factor); that heparin is inactive when in the presence of pure fibrinogen and thrombin and active only with the addition of plasma, has been known from the times of Howell and Holt[12]. However, the number and identification of plasma factors involved in coagulation are still in dispute, some authors identifying the factor with natural antithrombin, others postulating the existence of a separate factor (pro-antithrombin), a view now held as more probable. Another indication of union of heparin to plasma globulin is the anticomplementary effect of this substance.

If the main mechanism of bleeding control stays in plasma proteins rather than in blood elements like platelets, the effect described in this paper could be explained by the removal of one or more plasma components (by their union with heparin followed by their inactivation in a foreign surface) which are essential for the accomplishment of the series of events that culminate in the control of bleeding. On the other hand, the calcium deionization accomplished by citrates, not interfering with the essential globulins, has no effect on the hemostatic properties of the arterial blood when withdrawn from the organism. In this way, the

long persistance (6 or more hours) of the hemostatic abilities of citrated arterial blood when in contact with foreign surfaces can be explained.

This property of heparin to sensitize plasma globulins to a more or less rapid destruction when in contact with foreign surfaces, in contrast to decalcification by citrates which leaves the hemostatic properties of arterial blood intact, gives an important clue to the mechanism of blood changes outside the organism. The significance of the phenomenon of adsorption, taking from plasma some components and disrupting in this way the equilibrium between different individual plasma functional units, ought to be taken into consideration, with or besides the accepted platelet disintegration as the starting point of plasma changes culminating in coagulation (in case of natural blood) or in the loss of hemostatic properties, as pointed out in this paper. The observations carried out with heparinized blood, especially with rapid flowing blood in a foreign surface tube (Cruz and Oliveira[6]), showed facts that widen the interpretation field of plasma proteins and hemostasis.

Sketch of a Theory. If a foreign surface adsorbs some protein it could in this way unmask a property of some other protein that in natural conditions was checked by a particular protein configuration; it is not the removal of an inhibitory substance, but the removal, by adsorption, of a new protein complex formed by the presence of the strong electronegative heparin. This complex, never to be found in natural conditions, acts as an intermediate to allow adsorption by a foreign surface of constituents not adsorbed by such surfaces because of the absence of heparin. In order to explain why transfusion with heparinized plasma worked better than with citrated plasma in home hemophiliac patients, Van Creveld and Paulssen[16] point out that prevention of clotting by different anticoagulants results in physicochemical differences of prothrombin, since this coagulation factor is only partly adsorbed (70%) by barium sulfate in citrated plasma, whereas it is almost completely adsorbed (95%) in heparinized or oxalated plasma. The difference of heparinized plasma described by these authors could perhaps be enhanced by leaving the plasma in contact with a particular foreign surface for an adequate period of time. The observations described in this paper call attention to this rather neglected factor, that is, type of foreign surface and time of contact.

If we postulate that for normal hemostasis a correct balance between some plasma proteins is essential, then the controversy about the etiology of a hemorrhagic disorder, for instance, hemophilia, being due to a lack of a plasma factor (Tocantins, Pavlovsky, Seegers, Verstraete and Hecht, as quoted by Pavlovsky[15]: now generally the accepted view) or the presence of an inhibitory substance, loses much of its point. If correct balance of a pair of antagonistic substances is indeed essential to hemostasis, then the quantitative decrease of one of these substances will leave an excess of the other component which would thus act as a hemostatic inhibitor. On the other hand, if one of the substances happens to be present in higher quantities than in normal conditions, its excess in relation to its opponent would also act as a hemostatic inhibitor. In this way two different processes to achieve normalization of an unbalanced plasma could be admitted: 1) removal of the inhibitory substance in excess; 2) restoring the balance by addition of exact quantities of the antagonistic substance which was in relati e deficiency to its pair. Inhibition would then not be a

property of a determined substance; but any one of the substances that constitute the pair would act as an inhibitor when in excess in relation to the other.

This reasoning is, by the way, mandatory in enzymatic reactions. For a given effect, the amount of substrate is critical in many enzyme-substrate reactions; if the amount of substrate increases beyond a certain level, the reaction fades out. In this last case, substrate acts as an inhibitory substance that could be counteracted by a proportional increase of enzyme or withdrawal of the substrate to reach the optimum level again. Co-factors also act in many enzymatic reactions in optimum quantities, smaller or greater amounts having a similar effect in modifying the speed of the reaction. Such a pair, as postulated above, could be constituted by quantitative equilibrium of the substrate and co-factor in a type of enzymatic reaction that any one of them, when present in excess, would decrease the speed of reaction (inhibition).

If coagulation, as well as hemostasis observed with incoagulable blood, is based on equilibrium between some plasma components, and not on the total amount of the components involved, then the studies so far carried out are quite adequate. However, if the hemostatic aspects of blood in the organism depend not only on this equilibrium but also on the absolute quantities of the protein units active in hemostasis, then the present methods, that are unable to measure the correct amounts of particular hemostatic proteins without employing coagulation as a reference, are wholly inadequate. This inadequacy could explain some facts observed in hemophilia, when, in some phases of the disease, a normal coagulation time, *in vitro*, is accompanied by a serious picture of hemorrhagic disorder peculiar to this disease. Thus, a correct balance of two equally deficient substances would give a normal coagulation time *in vitro*, but this absolute deficiency of both factors would be responsible for the inability to control hemorrhages *in vivo*.

Summary. The behavior of heparinized arterial blood on hemostasis, as observed in the dog hind-leg preparation is markedly different from that of citrated arterial blood. When citrated, the blood keeps its hemostatic properties for many hours in contact with foreign surfaces. On the other hand, heparinized arterial blood taken from heparin-resistant donors loses these properties in a short time when contact is made with glass and, after a while, if contact with siliconed or paraffined surfaces is accomplished. If heparinized arterial blood is taken from heparin-labile donors, contact with siliconed or paraffined coated glass converts this non-hemostatic blood into fully hemostatic blood.

To observe the reversibility of this phenomenon, neutralization with protamine was carried out immediately after heparinization and contact with foreign surfaces. A marked difference in behavior was observed under these conditions. Blood heparinized *in vivo* kept its hemostatic capacities much longer, whereas blood heparinized *in vitro* irreversibly and almost immediately lost its hemostatic power.

The versatility of interaction of heparin with plasma globulins, especially with lipoproteins and the significance of these plasma components in the mechanism of normal and pathological hemostasis is discussed.

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SUMMARIO IN INTERLINGUA

Le Effecto de Heparinisate Sanguine Arterial Super le Hemostase in le Preparato de Gambas Posterior del Can

Le effecto de heparinisate sanguine arterial super le hemostase in preparatos de gamba posterior canin differe marcatemente ab illo de citrate sanguine arterial. Post citration, le sanguine mantene su proprietates hemostatic durante multe horas de contacto con superficies alien. Del altere latere, heparinisate sanguine arterial ab heparino-resistente donatores perde iste proprietates post breve intervallos de tempore quando illo se trova in contacto con vitro e post minus breve intervallos de tempore quando illo se trova in contacto con superficies siliconate o paraffinate. Si le heparinisate sanguine arterial es obtenite ab heparino-labile donatores, le contacto con vitro a revestimento siliconate o paraffiniate converte iste sanguine non-hemostatic in sanguine que es plenmente hemostatic.

Pro observar le reversibilitate de iste phenomeno, neutralisation con protamina esseva effectuate immediatemente post le heparinisation e le contacto con superficies alien. Sub iste conditiones un marcate differentia de comportamento esseva notate. Sanguine heparinisate in vivo manteneva su capacitates hemostatic durante multo plus longe periodos, durante que sanguine heparinisate in vitro perdeva su potentia hemostatic irreversibilemente e quasi immediatemente.

Es discutite le versatilitate del interaction de heparina con le globulinas del plasma, specialmente con lipoproteinas, e etiam le signification de iste componentes del plasma in le mechanismo de hemostase normal e pathologic.

THE EFFECT OF CORTISONE AND TRIAMCINOLONE ON THE IMMUNOLOGIC BACKGROUND AND THE COURSE OF EXPERIMENTAL GLOMERULONEPHRITIS*

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It is generally accepted that the corticosteroids have a marked influence on the formation of many antibodies. When given in large doses, cortisone and ACTH depress or suppress antibody formation (Bjorneboe, Fischel and Stoerk[1]). In contrast, adrenalectomy enhances antibody formation (Moll and Hawn[14]). The effect of cortisone on antibody formation is largely a question of dosage. Investigators who were unsuccessful with antibody suppression with cortisone (Mirick[15]) have in general used doses which were much too small to achieve the desired effect. From these studies it became evident that antibody suppression requires many times the amount of steroids necessary for anti-inflammatory action. On the other hand, it appears that certain antibodies cannot be suppressed by steroids. Overman and Hanan[16] showed that in the same animal cortisone was able to suppress completely the antibody formation against beef serum albumin while the antibody formation against sheep erythrocytes was not influenced to any degree. Fischel, Vaughan and Photopoulos[6] demonstrated that sufficient amounts of cortisone inhibit the rapid production of antibodies associated with a specific anamnestic response. The antibody already in circulation, however, is not all influenced by steroid medication and the disappearance rate of a passively administered antibody is not altered by cortisone (Fischel, Stoerk and Bjorneboe[5]). The effect of steroid on antibody formation varies widely in different species. Antibodies in rabbits appear readily suppressable by corticosteroids while it is much more difficult to influence antibody formation in guinea pigs (Germuth, Ottinger and Oyama[7]). Kass and Kendrick[9] were able to show that deoxyribonucleic acid (DNA) in lymph nodes of animals is not changed by the injection of cortisone but the pentose nucleic acids (PNA) are markedly decreased together with a decrease in numbers of immature lymphoid cells containing PNA with accumulation of macrophages. In their experimental setup, the mean weight of the lymph nodes decreased to about 35% of the normal weight as a conse-

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quence of the daily administration of large amounts of cortisone. After the administration of cortisone for 5 days, as much as 7 days were required for the reconcentration of PNA and for the size of the lymph nodes to return to the level of the controls. The findings which are in full agreement with similar studies of our own group are the basis of the prolonged intermittent steroid therapy with large doses of cortisone for nephrosis. It is aimed at a continuous depression of antibody formation without the production of too many Cushingoid features. While all newer corticosteroids are being widely tested for their effect on mineral and glycogen metabolism, their effect on antibody production is generally neglected and not studied on a comparative basis.

There is no proof at present that the anti-inflammatory effect or the effect on mineral or glycogen metabolism must necessarily parallel the effect on depression of antibody production. It appeared, therefore, interesting to study the effect of two different corticosteroids, cortisone acetate and 9-alpha-fluoro-16-alpha-hydroxy-prednisolone triamcinolone (Aristocort*), on a known antigen-antibody reaction with clinical sequelae namely, experimental glomerulonephritis produced in the rabbit by antirabbit kidney duck sera. Many observers consider this disease to be the best presently available model of the human disease, since its clinical, biochemical and morphologic features closely resemble human glomerulonephritis (Lange *et al.*[13,17]). Moll and Hawn[14] have studied the effect of ACTH and cortisone on experimental hypersensitivity using the fleeting glomerulitis produced by the antibody production against bovine gamma globulin as a model. Zollinger, Enderlin and Spuhler[19] have studied the effect of cortisone on experimental glomerulonephritis produced in rabbits by the injection of nephrotoxic duck sera. Using doses of 25 mg. per kg. of body weight daily, they achieved a marked or complete suppression of the disease. The lowest protective dose was 12.5 mg. cortisone per kg. per day. We have studied this experimental disease with similar results[12] and the studies reported below refer to more extensive investigations. In them, we compared the effect of cortisone and triamcinolone (Aristocort) at different dosage levels and on different facets of the disease, with the hope of finding a model for the comparison of different steroids used for the treatment of human cases of nephrosis or possibly glomerulonephritis.

Methods and Materials. The techniques used were described in detail in a previous communication.

1) Antirabbit kidney duck sera were produced in pekin ducks by 12 bi-weekly intraperitoneal injections of 10 ml. of a 10% suspension of rabbit kidney homogenate. The serum of 25 immunized ducks was pooled in these studies to secure uniformity of the antirabbit kidney duck serum (ARbKD).

In the studies comparing the effect of the transfusion of the serum of nephritic rabbits to rabbits sensitized with ARbKD shortly before, only the gamma globulin fraction of ARbKD was used for sensitization. This fraction was obtained by alcohol fractionation in the cold according to the method of Deutsch and Cohn[4]. It was found to be pure gamma globulin by paper electrophoresis. Similarly, only the gamma globulin fraction of the sera of nephritic rabbits, of rabbits given ARbKD gamma globulin together with cortisone or triamcinolone, and of rabbits immunized with unmodified duck serum gamma globulin, was transfused into recipient rabbits sensitized with ARbKD gamma globulin shortly before.

2) Male albino rabbits of the New Zealand strain, weighing approximately 5 pounds were used throughout. They were fed Purina pellets and water *ad lib.* The

*We are greatly indebted to Dr. Russel F. Cahoon of Lederle Laboratories for supplying us with generous amounts of Aristocort.

animals were weighed daily and the total daily urine output was examined for protein semi-quantitatively with 20% sulfo salicylic acid or quantitatively with the Biuret method (Weichselbaum[18]). Comparative determinations of the urinary proteins with the quantitative Biuret method and the semi-quantitative method using 20% sulfosalicylic acid, showed that 1+ sulfosalicylic acid corresponded to amounts between 100 mg. and 399 mg. per 100 ml., 2+ to 400 mg. and 799 mg., 3+ to 800 mg. to 2000 mg., 4+ to more than 2000 mg. per 100 ml. Wherever the urine specimen did not clearly fall into one of the above mentioned groups, a quantitative determination with Biuret was performed. Blood specimens were obtained as often as desired from the central ear artery according to the method of Cohen[3]. Every rabbit used in this study received on day 0 and day +1, one ml. of ARbKD per lb. of body weight intravenously or the corresponding amount of ARbKD gamma globulin only.

3) Blood urea nitrogen was determined according to the method of Karr[8]. Blood cholesterol was determined according to the method of Bloor, Pelkan and Allen[2]. Plasma proteins were determined according to the method of Weichselbaum[18].

4) Sodium and potassium were determined with the Process and Instruments Flame Photometer using lithium sulfate as an internal standard.

5) Precipitin tests were carried out according to the method described by Kay[10]; complement determinations as described by us previously[11].

All animals that survived to the sixteenth day after the first injection of ARbKD were sacrificed at that time and the kidneys were studied histologically. The same applied to the kidneys of animals which died spontaneously before the sixteenth day. All animals had at least three determinations of all biochemical and immunologic base values before the injection of the immune serum.

Results. Six rabbits received 2 intravenous injections of ARbKD in the amounts mentioned above but no other medication (Table 1). All of them came down with a 4+ proteinuria between the fifth and seventh day. None of the animals had less than at least 5 days of 4+ proteinuria followed by milder degrees of proteinuria on the subsequent days. Four animals were sacrificed on the sixteenth day, one died on the twelfth day and one on the fourteenth day after the first injection, in uremia. Three animals had a rise of BUN to between 50 mg. and 100 mg. and 3 to above 100 mg. per 100 ml. The average of the maximal precipitin titers against duck serum of these rabbits was 1:45.3. The lowest titer found was 1:16 and the highest of 1:64. Complement fell to decidedly subnormal levels in all 6 animals within 12 hours prior to the onset of proteinuria.

Eleven animals received cortisone acetate suspension 20 mg. per kg. per day intramuscularly in 2 divided doses starting simultaneously with the intravenous injection of the ARbKD. This dose of cortisone was found to be the best protective dose in previous studies on 76 rabbits, for larger doses led to early death of many animals. With this medication, one animal showed no proteinuria throughout the observation. Three showed a maximal proteinuria of 1+, two of 3+ and one of 4+. The onset of proteinuria was markedly delayed as compared to the control group in most of the animals. Four animals were sacrificed on the sixteenth day, 2 died on the ninth day, and one the tenth day, one on the thirteenth day and 2 on the fourteenth day after the first injection. In this group 7 animals showed no rise of the BUN to abnormal levels, two had a rise to levels between 50 mg. and 100 mg. and 2 to above 100 mg. per 100 ml. The average of the maximal precipitin titers against duck serum was 1:29. The lowest titer found was 1:16 and the highest, 1:32. Complement fell in all animals at the onset of disease but only very slightly in the one animal that had no proteinuria whatsoever.

Six rabbits received aqueous triamcinolone (Aristocort) suspension 0.3 mg. per kg. per day intramuscularly,

TABLE 1.—INFLUENCE OF DIFFERENT AMOUNTS OF TRIAMCINOLONE (ARISTOCORT) AND CORTISONE ON PROTEINURIA, BUN, SERUM COMPLEMENT, ANTIBODIES AGAINST DUCKSERUM AND SURVIVAL IN RABBITS WITH EXPERIMENTAL GLOMERULONEPHRITIS PRODUCED BY ANTIRABBIT KIDNEY DUCKSERUM INJECTIONS.

Medication	*No. of Animals*	*Maximal Proteinuria* 0 1+ 2+ 3+ 4+	*BUN Maximal*			*Serum complement subnormal*	*Antibodies (precipitins) against Duckserum average titer 1:*	*Survival to day +16 (day of sacrifice)*
			Normal	*50 to 100 mg./100 ml.*	*more than 100 mg./100 ml.*			
ARbKD i.v. only	6	6		3	3	6/6	45.3	4/6
ARbKD i.v. + Cortisone 20 mg./kg./day i.m.	11	1 3 4 2 1	7	2	2	10/11	29.0	4/11
ARbKD i.v. + Triamcinolone (Aristocort) 0.3 mg./kg./day i.m.	6	1 2 1 2	5	1		5/6	50.0	5/6
ARbKD i.v. + Triamcinolone (Aristocort) 1.0 mg./kg./day i.m.	9	1 3 2 1 2	8		1	9/9	32.0	9/9
ARbKD i.v. + Triamcinolone (Aristocort) 3.0 mg./kg./day i.m.	6	2 1 1 2	6			6/6	26.0	5/6

starting simultaneously with the injection of the ARbKD. One of these animals showed no proteinuria, two a 2+, one a 3+ and two a 4+ maximal proteinuria. The 4+ proteinuria extended to 3 days in one animal and was present for one day in the other animal. Five animals were sacrificed on the sixteenth day, while one died on the thirteenth day. Five animals had normal BUN values throughout, while one animal had a rise of BUN to 95 mg. per 100 ml. This is the animal which died on the thirteenth day. The average of the maximal precipitin titers against duck serum was 1:50. The lowest titer found was 1:16 and the highest, 1:64. Complement levels fell in all animals to subnormal levels except in the one which did not show any urinary abnormalities throughout the course of the disease.

Nine rabbits received triamcinolone, 1 mg. per kg. per day intramuscularly starting simultaneously with the injection of ARbKD. One animal showed no proteinuria during the course of his disease. Three had a maximal proteinuria of 1+, two of 2+, one of 3+ and two of 4+, the latter lasting for not more than 3 days. All animals were sacrificed on the sixteenth day. None died spontaneously. The BUN remained normal in 8 and rose to a peak level of 156 mg. per 100 ml. in one animal. The average of the maximal precipitin titers against duck serum was 1:32 which was the maximal titer in all of the animals. Complement levels fell in all animals but to a much lesser degree than in the controls.

Six rabbits received a daily injection of aqueous triamcinolone suspension 3 mg. per kg. per day intramuscularly, starting simultaneously with the injection of the ARbKD. Two animals had a 1+, one a 2+, one a 3+ and two a 4+ proteinuria. This 4+ proteinuria lasted in both animals for 2 days only. Five animals were sacrificed on the sixteenth day while one died on the eighth day. The BUN remained normal in all of them. The average of the maximal precipitin titers against duck serum was 1:26, the lowest titer found was 1:16, the highest 1:32. Complement fell in all animals with the onset of disease, but to a very slight degree only.

It was conspicuous that 50% of the animals on cortisone medication showed a marked fall in serum potassium, below 3 mEq. beginning about the seventh day after injection. No such fall was observed in the untreated controls or in any of the animals on triamcinolone therapy.

We showed previously[13] that in contrast to Kay's[10] earlier contention, it is not the antibody against unmodified duck serum which produces experimental glomerulonephritis, but rather the more specific antibody against the kidney localizing fraction of such a serum. The transfusion of 50 ml. of serum of a rabbit with acute glomerulonephritis due to an injection of ARbKD or its gamma globulin fraction into a rabbit sensitized 24 hours before with ARbKD leads to an immediate acute glomerulonephritis (passive transfer of disease producing antibody). In contrast, the transfusion of 50 ml. of serum of a rabbit injected with an equal amount of unmodified duck serum or its gamma globulin into a rabbit sensitized 24 hours before with ARbKD does not lead to an immediate disease. The glomerulonephritis occurs in the latter situation only after 5 to 7 days, the interval after which the disease would occur when ARbKD were given alone.

In order to see whether the *specific* antibody is also depressed, just as the antibody against unmodified duck serum, the following experiments were carried out.

GROUP 1. Six rabbits were given 100 mg. per kg. of ARbKD gamma globulin intravenously. All of them came down with a 4+ proteinuria and uremia between the fifth and seventh day. All were exsanguinated by cardiac puncture at the end of the seventh day. The sera were pooled and the gamma globulin fraction was obtained by alcohol fractionation in the cold.

GROUP 2. Similarly a group of 5 rabbits were given 100 mg. per kg. of ARbKD gamma globulin intravenously, but simultaneously with it, 2 daily injections of 1.5 mg. per kg. of triamcinolone suspension i.m. One of these animals showed no proteinuria by the seventh day, one showed a 1+ proteinuria, two a 2+ proteinuria and one a 3+ proteinuria. All were exsanguinated at the end of the seventh day, their sera pooled and the gamma globulin fraction was obtained by alcohol fractionation in the cold.

GROUP 3. A group of 4 rabbits were given 100 mg. per kg. of unmodified duck serum gamma globulin intravenously. None of them showed any proteinuria until the end of the seventh day when they were exsanguinated, their sera pooled and the gamma globulin fraction obtained.

GROUP 1-A. Eight rabbits received 100 mg. per kg. of ARbKD gamma globulin intravenously and 24 hours later 200 mg. per kg. of the gamma globulin of the serum pool of the nephritic animals of Group 1 (passive transfer of antibody). Three to 4 plus proteinuria appeared within 24 hours in 4 animals; in 48 hours in one, and within 72 hours in 2, while one rabbit became anuric for 3 days and the urine on the fourth day showed a 4+ proteinuria.

GROUP 2-A. Seven rabbits received 100 mg. per kg. of ARbKD gamma globulin intravenously and 24 hours later 200 mg. per kg. of the gamma globulin of the serum pool of the animals of group 2 (ARbKD + triamcinolone). One of these came down with a 4+ proteinuria on the fifth day, 3 with a 3 to 4+ proteinuria after 6 days, while in the remaining 3, seven days elapsed before proteinuria appeared. This seems to indicate that in this group no passive transfer of nephritic antibody had taken place, since the serum pool of the triamcinolone treated animals apparently did not contain such antibodies or in insufficient quantities to produce disease. The appearance of nephritis between the fifth and seventh day is the normal interval for appearance of disease after the injection of the sensitizing dose.

GROUP 3-A. Two animals received 100 mg. per kg. of ARbKD gamma globulin intravenously and 24 hours later 200 mg. per kg. of the gamma globulin of the serum pool of the animals of Group 3 (unmodified duck serum). One animal showed a 4+ proteinuria, 6 days, and one, 7 days after the injection of the ARbKD gamma globulin, the normal interval for appearance of disease without passive transfer of antibody. It thus appears as demonstrated previously[13] that antibodies to unmodified duck serum gamma globulin do not play any role in the immune mechanism of experimental glomerulonephritis.

Discussion. The data presented seem to indicate that triamcinolone (Aristocort) as well as cortisone depress antibody formation. It appears that 20 mg. per kg. per day of cortisone exerts approximately the same antibody suppressing effect as 1 mg. per kg. per day of triamcinolone; 0.3 mg. of triamcinolone, however, does not seem to produce any suppression of antibody formation which is similar to the results which we previously obtained using 5 mg. of cortisone only. It should be kept clearly in mind, however, that the anti-

body against duck serum is not the antibody which produces the disease. As we could show previously the antibody against the *specific factor* in duck serum which is directed against and localizes on the basement membrane of the glomerulus ("localizing factor") is the disease producing antibody. Since this antibody, however, cannot be measured directly, we initially resorted to the determinations of the readily measurable antibodies against unmodified duck serum protein.

The experiments using the passive transfer of antibody by the transfusion of nephritic blood or its gamma globulin fraction, permit an objective estimation of the presence or absence of such nephritogenic antibodies. The fact that these antibodies are absent or markedly diminished in the blood of triamcinolone treated animals, indicates the effect of this compound on the formation of the specific nephritogenic antibody.

The effect of such steroid medication on the proteinuria resulting from the glomerulonephritis produced by the injection of ARbKD is not as proportional to dosage as is the effect on antibody suppression. One may speculate that the anti-inflammatory effect of the steroids is already exerted at a much lower dose and expresses itself in a diminished proteinuria in addition to the diminished antigen-antibody reaction which occurs at considerably higher levels.

The survival of animals receiving cortisone, nevertheless, was worse than those not receiving any medication. It appears interesting to note that many of the animals on cortisone medication had a severe potassium depletion which might have been the cause of death in many of them. No such potassium depletion was observed in any of the animals receiving triamcinolone or in the untreated controls. The survival rate of the animals on triamcinolone is better than the survival of the controls and much better than the survival of the animals treated with cortisone. The most outstanding difference between the group not treated with steroids and the group treated with steroids at varying levels was the diminished number of animals which became uremic in the steroid treated group. While all of the untreated animals were uremic at one time during the study, only 2 of 21 animals treated with triamcinolone showed transient uremia while 4 of the 11 animals treated with cortisone showed such uremic episodes.

Complement fell in all animals except one which is well understandable by the fact that all animals in spite of steroid therapy developed some degree of antibody formation thus permitting the complement binding antigen-antibody reaction to take place leading to lowering of the complement level. The only animal which did not show such a fall in complement level also had no clinical disease and the lowest rise in antibody titer of the entire group.

The histologic and histochemical findings in the treated and untreated animals will be reported separately. It can be stated, however, that they were in good agreement with the clinical findings.

It appears from these studies that the steroids exert a marked antibody suppressing effect only when given in large doses and that the beneficial effect of steroid medication on experimental glomerulonephritis must be considered a composite one, consisting of antibody suppression as well as of an anti-inflammatory effect, whereby triamcinolone seems to be approximately 20 times as effective as cortisone mg. per mg., and seems to be devoid of certain side effects, especially

potassium loss, which killed many animals in the group treated with large doses of cortisone.

Summary. Cortisone acetate and triamcinolone depress antibody formation to duck serum in rabbits injected with nephrotoxic antirabbit-kidney duck serum. The specific antibody producing experimental glomerulonephritis, namely the antibody against the localizing fraction of the nephrotoxic serum is also depressed as shown by the transfusion of serum of "nephritic" animals with and without treatment with cortisone acetate and triamcinolone. Transfusion of the serum of untreated nephritic rabbits resulted in immediate nephritis in sensitized animals, while the transfusion of serum of cortisone and triamcinolone treated "nephritic" rabbits did not produce disease in sensitized animals. Experimental glomerulonephritis is ameliorated in the steroid treated animals not only on account of the depression of antibody formation but also by direct anti-inflammatory action.

Triamcinolone is approximately 20 times as effective as cortisone acetate in suppressing experimental glomerulonephritis. Uremia which occurs with regularity in the untreated group occurred in only 4 of 11 rabbits treated with cortisone acetate and in only 2 of 20 animals receiving sufficient amounts of triamcinolone.

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(Interlingua on page 446)

SYSTEMIC CONTROL OF CUTANEOUS FUNGOUS INFECTIONS*†

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The ringworm type of superficial fungi almost never invades below the dead cornified layers of the skin (Fig. 1*A*). The tuberculin type of immunologic response which the dermatophytes induce cannot account for their surface location, nor can metabolic preference for keratin or for dead tissue. A clue to the mechanism came from the demonstration by Lorincz, Priestley and Jacob that fungi within a dialysis bag were inhibited when suspended in fresh human serum[5].

In our laboratory, sheets of skin were grown as an organ culture on the surface of nutrient media[2] (Fig 2). By varying the constituents of the media, the fungi could be allowed to invade living cells (Fig. 1*B*) or be kept confined to their normal outer habitat beyond the epidermal barrier. For the first time "ringworm" infections could be produced *in vitro* and some of the host factors explored. Fresh sera of many species of animal were found inhibitory; heating and dialysis destroyed the activity. Serum protein fractions including gamma globulin were inactive.

In vitro assays of many sera indicated that the antidermatophyte activity was present at birth and did not change appreciably with age (Roth *et al.*[6]) (Fig. 3). It was in distinct contrast with the inhibitory serum activity which we measured against the yeast, *Candida albicans*. The anti-Candida (antimonilial) effect is absent at birth, is thermostabile at 56° C. and declines in patients with acute blood dyscrasias (Roth and Goldstein[7]). During our studies of these two distinct, inhibitory activities of serum, a patient was admitted to the dermatology service with a singular lack of the antidermatophyte effect. The patient had widespread subcutaneous granulomas and abscesses in which only *Trichophyton rubrum* could be demonstrated (Fig. 4*A*,*B*). Because this organism ordinarily causes only superficial tineas of the skin and nails, it seemed to be proof of the hypothesis that the serum factor is important in preventing invasion.

For months we made fruitless attempts to slow the patient's life-threatening invasive *T. rubrum* infection. On August 16, 1958, Gentles reported that griseofulvin was an orally effective antifungal agent in guinea pigs[4]. On September 15, 1958, treatment with the hitherto untried antibiotic was started on our patient and his spectacular re-

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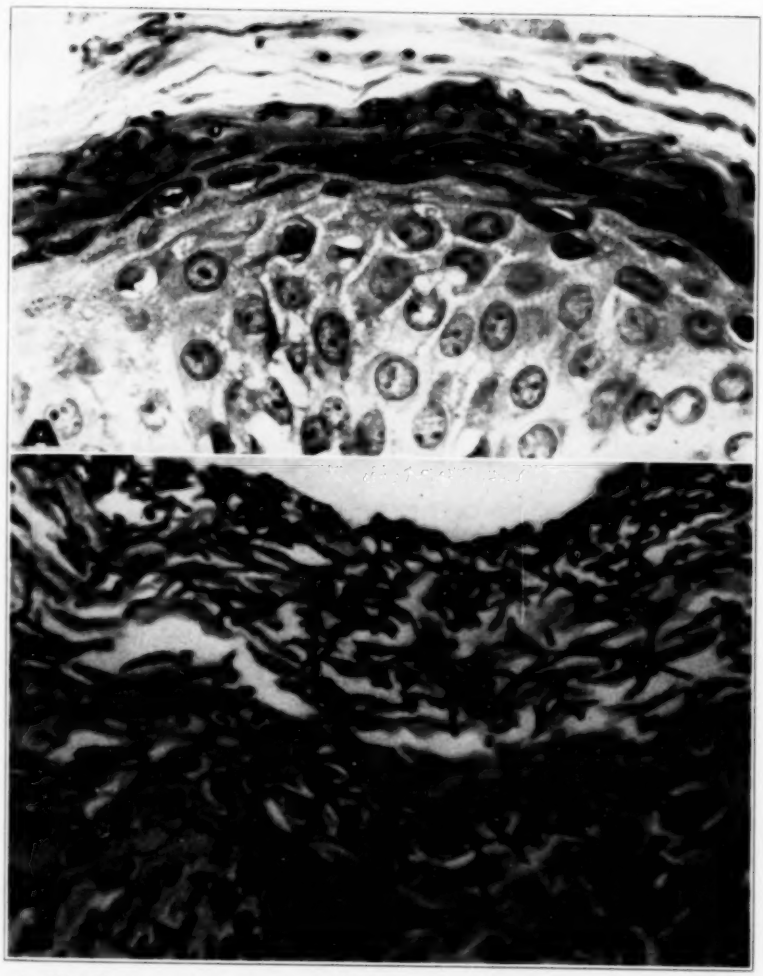

Fig. 1.—*A*, Histologic section of superficial fungous infection demonstrating mycelia failing to penetrate below stratum corneum (PAS-hematoxylin). *B*, Histologic section of same skin after incubation *in vitro* on surface of serum-free medium for 96 hours demonstrating active invasion of living epithelium by the fungus (PAS-hematoxylin).

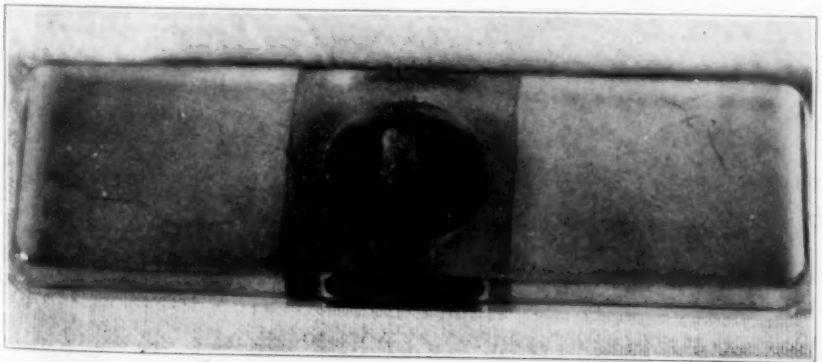

Fig. 2.—Organ culture device. The slide has a parallel side well filled with liquid culture medium and covered with lens paper to support the sheet of skin. It is handled and incubated within a petri dish.

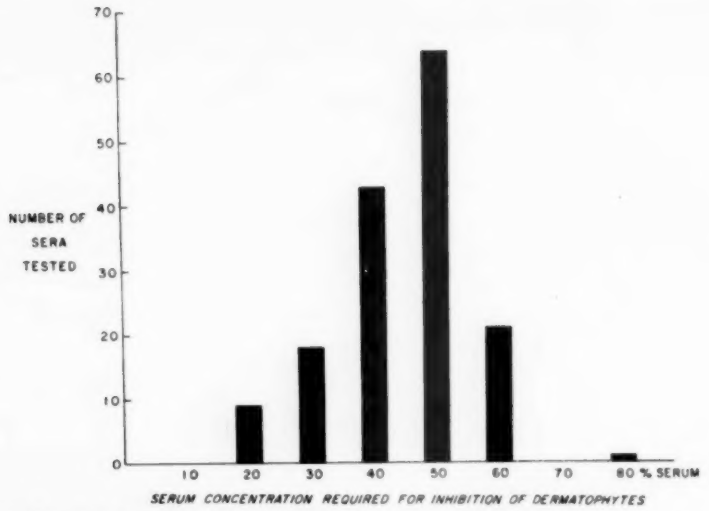

Fig. 3.—Antidermatophyte titers of 156 human sera measured as fungistasis of a pellet of *T. rubrum* incubated for 12 hours.

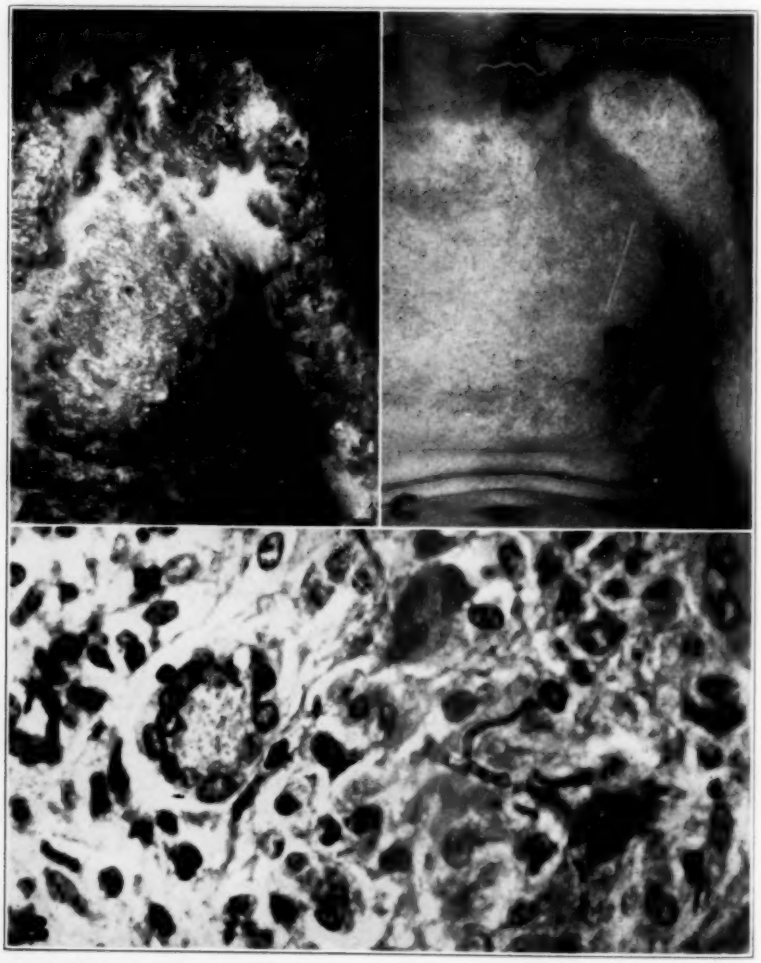

Fig. 4.—*A*, Multiple granulomas and abscesses caused by *Trichophyton rubrum* threatening the patient's life. *B*, Histologic section of subcutaneous granuloma showing mycelia (PAS-hematoxylin). *C*, After oral griseofulvin all lesions subsided.

sponse (Fig. 4C) without side-effects catapulted griseofulvin to world attention (Symposium[9]). Much had to be learned in the clinic and the laboratory before the drug could be used wisely and safely (Blank *et al.*[1,3], Symposium[9]).

In spite of its unique curling and destruction of the growing tips of mycelia (Fig. 5), it proved to be a fungistatic rather than fungicidal antibiotic and to be effective against only the infections caused by species of the three genera: Trichophyton, Microsporum and Epidermophyton (Roth, Sallman and Blank[8], Symposium[9]). Spectrophotofluorometric assays showed maximum blood level in 4 hours and persistence in serum for 72 hours. To determine its all important movement to the surface of the skin, a bioassay technique devised for measuring normal antifungal activity *in situ* on a subject's arm was modified to measure griseofulvin (Symposium[9]) (Fig. 6). The drug appears to produce its favorable clinical effect by inhibiting the fungi and causing them to be shed with the normal outward growth and desquamation of the skin, hair and nails. Oral griseofulvin (1.0 gm. per day) must be continued until the condition is healed (see Figs. 7, 8, 9, 10), except for infection of the scalp hair, which usually is cured with a single 3.0 gm. dose. The efficacy and safety of griseofulvin are reported in great detail in the vast literature which has appeared in the past year (Symposium[9]).

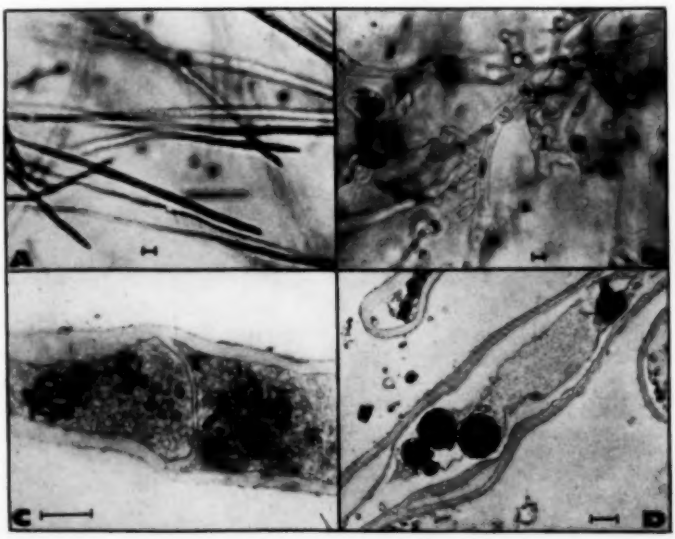

Fig. 5.—*A*, Hyphal tips of *Trichophyton rubrum* growing in liquid medium. *B*, Same as *A* but with griseofulvin in the medium. The swelling, distortion and "curling" of the hyphae is characteristic. *C*, Normal mycelium as in *A* with septum, mitochondria and other cytoplasmic details shown with the electron microscope. *D*, Same as *B* but with the electron microscope it is evident that griseofulvin causes a loss of cytoplasmic contents, appearance of huge lipid granules and cell wall distortion with death of the young growing cells. The older cells are less affected.

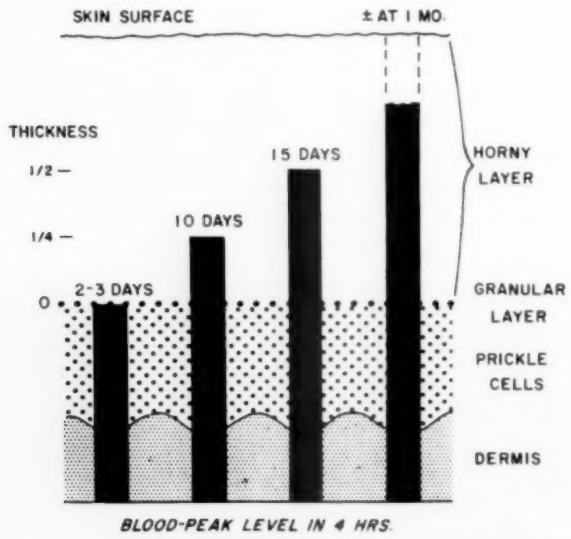

Fig. 6.—Bioassay of griseofulvin determined *in situ* on the flexor surface of the forearm. Measurement is made of the inhibition of growth of germ tubes from macroconidia placed on the skin after varying amounts of stripping with cellophane tape to reach deeper levels of the stratum corneum.

Fig. 7.—*A*, Tinea of the axilla caused by *Trichophyton rubrum*. *B*, After 4 weeks of oral griseofulvin, 1.0 gm. per day.

Summary. Dermatophytic fungous infections characteristically are superficial because thermolabile dialyzable serum factors repel deeper invasion. A patient with a low titer of these serum antidermatophyte factors developed rare subcutaneous abscesses produced by *Trichophyton rubrum*. The spectacular response of this patient to the hitherto untried antibiotic, griseofulvin, catapulted this drug to world-wide attention.

Subsequent studies confirmed the impression that griseofulvin, 1.0 gm. a day by mouth, would cause clearing of many stubborn and heretofore incurable fungous infections of skin, hair and nails. Differences in response of some patients may reflect differences in absorption from the gastrointestinal tract

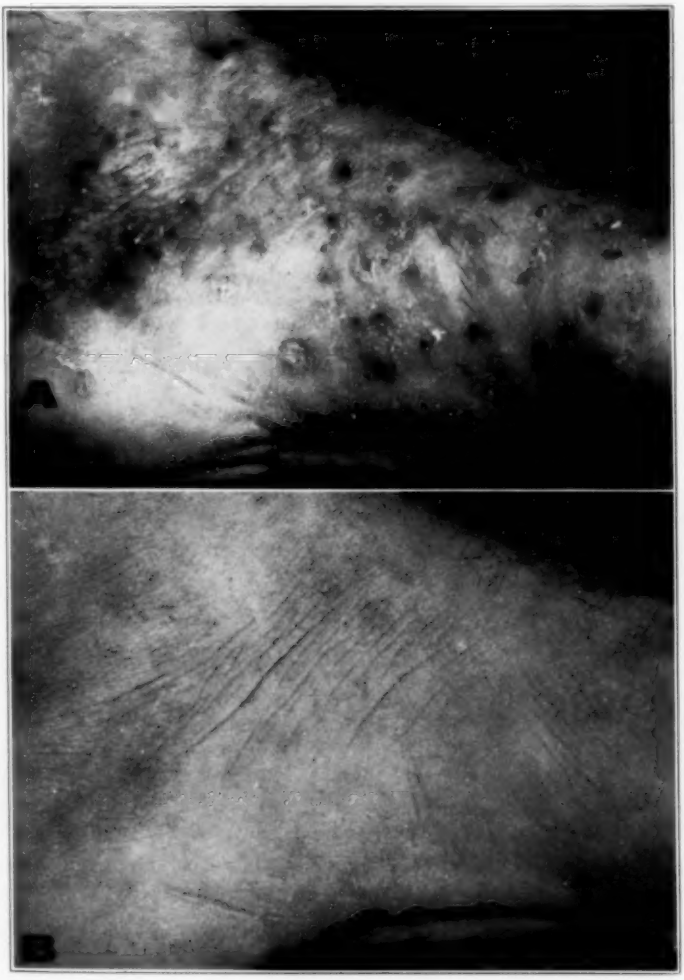

Fig. 8.—*A, Tinea pedis* caused by *Trichophyton rubrum*. *B*, After 6 weeks of oral griseofulvin, 1.0 gm. per day.

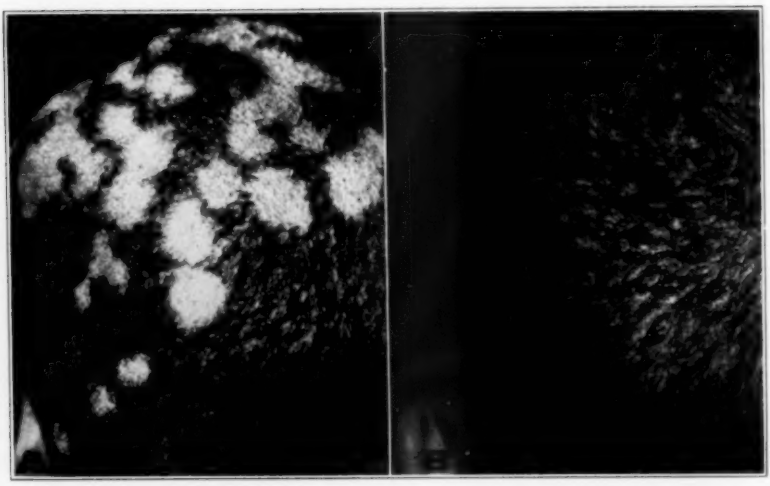

Fig. 9.—*A, Tinea capitis* caused by *Microsporum audouini*. *B*, Seven weeks after a single oral dose of griseofulvin; 3.0 gm. given once will cure most scalp ringworm. In 10 to 20% the dose may have to be repeated once or twice at monthly intervals.

Fig. 10.—*A*, Onychomycosis caused by *T. rubrum* of 20 years' duration and unresponsive to previous surgery and local treatment. *B*, After 5 months of 1.0 gm. of griseofulvin per day.

of the drug. Resistant strains of organisms have so far been rare. A bioassay technique developed for measuring the movement of griseofulvin through the skin structures *in situ* demonstrates the slow outward movement of griseofulvin with newly formed keratin. Electron microscopy of affected growing mycelial tips exposed to griseofulvin reveals profound cytoplasmic and cell wall changes but Warburg studies indicate that the metabolism of the mass of older hyphae is little affected by griseofulvin. The drug is considered fungistatic rather than fungicidal.

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SUMMARIO IN INTERLINGUA

Defensa Intrasystemic Contra Cutanee Infectiones Fungal

Infectiones dermatophytic es characteristicamente superficial, proque invasiones plus profunde es repellite per thermolabile e dialysabile factores seral. Un patiente con basse titros de ille factores antidermatophytic in le sero disveloppava un typo rar de abscessos subcutanee per *Trichophyton rubrum*. Le responsa frappante de iste patiente al previemente non testate antibiotico griseofulvina lanceava ille droga in le lumine de un attention mundial.

Studios subsequente confirmava le impression que griseofulvina in un dosage de 1 g per die per via oral resultarea in le resolution de multe tenace e previemente incurabile infectiones fungal de pelle, capillo, e ungulas. Differentias in le responsa de varie patientes reflecte possibilemente differentias in le absorption del droga ab le vias gastrointestinal. Racias resistente del organismo ha remanite rar. Un technica de bioessayage pro mesurar le movimento de griseofulvina a transverso le pelle in sito demonstra le lente migration extrorse de grisofulvina con novemente formate ceratina. Microscopia electronic de afficite punctas mycelial in stato de crescentia revela durante le exposition a griseofulvina profunde alterationes del cytoplasma e del pariete cellular, sed studios warburgian indica que le metabolismo del massa de hyphas plus matur es pauco afficite per griseofulvina. Es opinate que le droga es fungistatic plus tosto que fungicida.

ION EXCHANGE RESINS IN THE FORMULATION OF SUSTAINED RELEASE MEDICATION

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and

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Useful long-acting medications are those that provide a predictable, consistent and reproducible sustained drug release. These medications release a quantity of drug that is therapeutically effective throughout the extended period of activity. The initial drug release is sufficient to produce an immediate effect. Whenever possible their rate of release corresponds to the daily cyclic pattern of the illness. Moreover, they do not build-up a significant concentration of residual drug under conditions of intestinal obstruction. These are the unique advantages of sustained-release oral medications which have long been recognized by both the medical and pharmaceutical professions.

Currently available long-acting drugs utilize a variety of techniques to effect a prolonged release. Thus, molecular modifications, chemical complexes, coated granules, coated tablets, layered tablets, resin and wax matrices and synthetic organic resin complexes are all being used to reduce the rate of absorption or availability of the active drug. Two different principles are utilized in the formulation of drugs with synthetic organic resins. One method incorporates the drug within the lattice structure of the resin to impede its diffusion and the other, in addition to the restricted diffusion, effects a predictable release of the drug in the gastrointestinal tract by means of ion exchange. The extensive application of the ion exchange principle in the formulation of oral medication has created a need for understanding the chemical factors associated with the use of ion exchange resins.

The ion exchange resins which are employed in the preparation of sustained release medications are chemically stable, high molecular weight polymers having a definite cross-linkage and possessing chemically active groups which effect ionic transfer (Fig. 1). They are non-toxic, insoluble entities which resist enzymatic degradation. These resins are capable of a drug uptake sufficiently adequate to achieve the desired therapeutic effect.

In the preparation of drug resinates, the reaction of a drug with a resin is a physico-chemical reaction exhibiting a high degree of reproducibility. It is possible to obtain drug resinates of constant quality if the optimal conditions of drug concentration, the degree of resin saturation, and time of reaction are known. These variable factors can be determined, however, only by meticulous and exacting laboratory study.

The effect of pH change within the approximate total physiological cationic concentrations found in the stomach of man is shown in Table 1. It will be noted that an appreciable amount of drug is released in an acidic medium even in the absence of sodium ions, which is not likely to occur in the

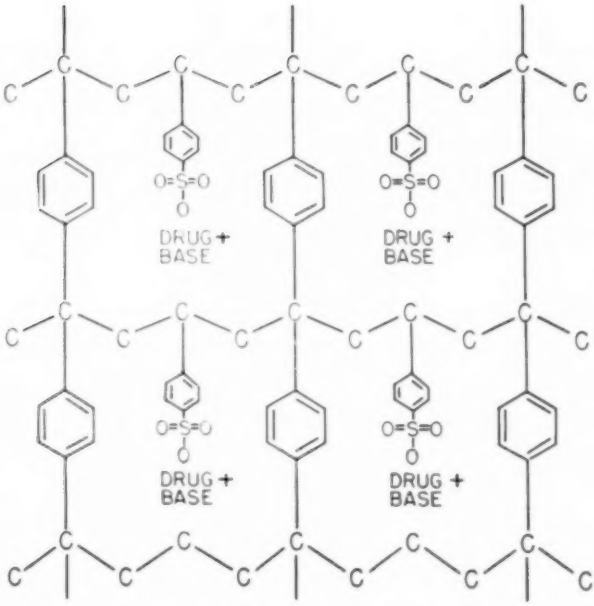

Fig. 1.—Diagrammatic presentation of resin-drug complex.

TABLE 1.—EFFECT OF IONIC CONCENTRATION ON RATE OF RELEASE

Ionic Concentration					*% of Drug Released During*
H^+	Na^+	Ca^{++}	Cl^-	*pH*	*First Hour*
0.0997	—	—	0.0997	1.11	24.7
0.0990	0.001	—	0.100	1.13	21.7
0.0752	0.0342	—	0.1094*	1.19	39.9
0.001	0.099	—	0.100	3.02	47.3
0.001	0.089	.01	0.1	3.08	49.4
0.0001	0 0999	—	0.1	3.78	43.5
0.00001	0.09999	—	0.10000	5.11	40.7
—	0.100	—	0.100	5.53	43.7
—	0.1031	—	0.100	7.32	44.7

*U.S.P. gastric juice less enzymes.

stomach. On the other hand variations in pH from 1.2 to 7.3 have only slight effect on the rate of release of the drug from the drug-resin complex. This uniformity of release is particularly important when the drugs such as the anticholinergics affect acid secretion. The addition of small amounts of calcium ions, such as might be encountered after the ingestion of an anti-acid, likewise has little effect.

rapid rate of release. The resin lattice is formed by the divinyl benzene cross-linkage of the styrene polymer and thus the degree of cross-linkage determines the lattice density. Increased lattice density reduces the rate of release.

A comparison of release of amphetamine or methamphetamine from a resin matrix with that of an ion-exchange resin is illustrated in Table 2. It can be seen from these data that the

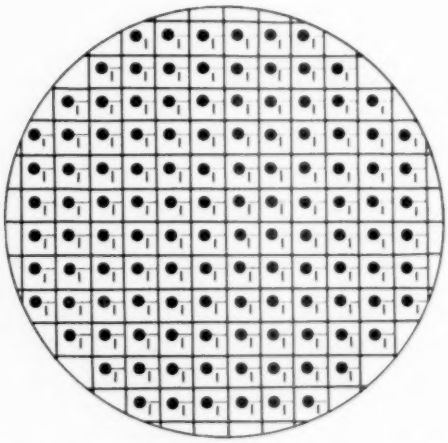

Fig. 2—Two dimensional diagrammatic presentation of lattice structure of a resin bead.

The rate of release of a drug from an ion exchange resin, like all chemical reactions, is influenced by its position in the electromotive series of Hofmeister and the Law of Mass Action (Kunin[9]). Other factors, however, such as ionic size, configuration of the drug, resin particle size, lattice density and the degree of drug saturation of the active groups exert an important influence on the rate of release. The lattice structure of the resin particle is shown schematically in Fig. 2. It is within this lattice that the drug moiety must be free to move both by diffusion and by electrovalent exchange. It is evident that a higher degree of saturation of the active groups produces a more

drug incorporated in a resin matrix can be readily eluted in water or gastric juice. In contrast, the ion-exchange resin drug complex releases only in the presence of electrolytes such as those found in the gastric and intestinal juices.

A tabulation of the various types of sustained release preparations and the factors which affect their drug availability is presented in Table 3. In the majority of these medications, as many as 9 variable factors influence the release of the active drug. On the other hand, the drug release from an ion exchange resin complex is influenced by a single relatively constant factor. Consequently, the rate of release from

the latter preparation can be predicted with a high degree of accuracy.

In-vivo prolongation of drug activity has been demonstrated experimentally in rats, guinea pigs and dogs with a variety of drug resinates (Becker[1], Becker and Hays[2], Swift[11]). More recently a number of clinical studies have been published demonstrating effective sustained release of several therapeutic agents prepared as ion-exchange resin complexes (Cass[3], Cass and Frederik[4,5], Chan and Hays[6], Freed *et al.*[7,8], LeRiche[10], Townsend[12]). These therapeutic agents, namely, cough suppressants, antihistaminics, anoretics and analgesics as drug resinates, have provided the patient and clinician with necessary dependable sustained release oral medication.

Summary. Sustained release medications have unique advantages long recognized by the medical and pharmaceutical professions. As many as 9 vari-

TABLE 2.—COMPARISON OF RELEASE FROM RESIN MATRIX AND ION-EXCHANGE RESIN COMPLEX

Preparation	*Elutrient*	*1 hr.*	*2 hr.*	*3 hr.*	*4 hr.*	*5 hr.*	*6 hr.*	*6 hr. Total*
Resin impregnated matrix	Distilled water only	49.7	14.5	8.3	5.8	4.2	2.7	85.2
	Simulated gastric juice	52.8	14.5	11.4	6.6	4.8	2.7	92.8
Ion exchange resin	Distilled water	0.2	0	0	0	0	0	0.2
	Simulated gastric juice	35.9	19.7	13.7	8.3	6.1	3.8	87.5

TABLE 3.—TYPES OF SUSTAINED RELEASE PREPARATIONS AND FACTORS WHICH AFFECT THEIR DRUG AVAILABILITY

	Factors grossly affecting drug availability from sustained release tablets or capsules								
	Electrolyte Conc.	*Electrolyte Volume*	*pH*	*Surface Tension*	*Temperature*	*Composition of Disintegrating Matrix*	*Agitation (Degree or Type)*	*Enzymes*	*Time*
1. Mixture of several coated granulations of different solution rates.	yes	yes	yes	yes	yes	yes	yes	yes	yes
2. Multi-layer tablets—layers of different solution rates.	yes	yes	yes	yes	yes	yes	yes	yes	yes
3. Enteric coated core within tablet	yes	yes	yes	yes	yes	yes	yes	yes	yes
4. Coated pellets	yes	yes	yes	yes	yes	yes	yes	yes	yes
5. Chemical complex requiring hydrolysis	yes	yes	yes	no	yes	no	no	no	yes
6. Coated pellets in wax-type matrix	yes	yes	yes	yes	yes	yes	yes	yes	yes
7. Drug impregnated resin matrix	yes	yes	yes	yes	yes	no	yes	no	yes
8. Ion exchange resin complex	yes	no	no	no	no	no	no	no	no

able factors may influence the release of the active drug from various long-acting preparations.

The chemical factors associated with the action of ion exchange resinates are discussed in detail. Only a relatively constant factor influences drug release from a given ion exchange resin: the concentration of electrolyte. Hence, the rate of drug release from ion exchange resinates can be predicted with a high degree of accuracy.

Published animal and clinical data demonstrate that therapeutic agents prepared of ion exchange resin complexes provide dependable sustained release oral medication.

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SUMMARIO IN INTERLINGUA

Resinas a Excambio de Iones in le Formulation de Medicationes a Liberation Continue

Medicationes a liberation continue possede avantages particular que es recognoscite depost longo per le professiones medical e pharmaceutic. Non minus que 9 factores variabile pote influentiar le liberation del droga active ab varie preparatos a action perdurative.

Es discutite in detalio le factores chimic que es associate con le action de resinatos a excambio de iones. Solmente un relativemente constante factor influe super le liberation del droga ab un specific resina a excambio de iones, *i.e.* le concentration del electrolytos. Per consequente le rhythmo del liberation del droga ab resinatos a excambio de iones pote esser predicite con alte grados de accuratia.

Le publicate reportos de observationes experimental in animales e etiam de observationes clinic demonstra que agentes therapeutic preparate con complexos de resina a excambia de iones representa un forma de medication oral a liberation continue que es digne de confidentia.

THE CASE FOR EUTHYROID HYPOMETABOLISM

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The existence of a certain group of patients whose clinical symptoms and low basal metabolic rates (BMR) suggest hypothyroidism, and yet, who derive no benefit from thyroxine therapy, has long been known (Kirk and Kvorning[25], Means[38]). Such cases are generally regarded as having either a functional lowering of their metabolism secondary to malnutrition or psychoneurosis, or else, compromising the lower fraction of a normal distribution curve of basal metabolic rates. A rather constant feature of such patients has been the presence of anxiety states, labile emotions, and easy fatiguability (Thurmon and Thompson[51]). Since therapeutic trials on L-thyroxine or desiccated thyroid were either ineffectual, or else, poorly tolerated, such psychodynamic symptoms were believed to be the cause of the low metabolism rather than the consequence of it. The isolation and identification of the potent, naturally occurring thyroid hormone, L-triiodothyronine (T-3), in the blood by Gross and Pitt-Rivers[18], and in the thyroid gland by Roche, Lissitsky and Michel[43] in 1952, made available a second thyroid hormone for testing in patients with disturbed metabolic function. In 1955, a report by Kurland, Hamolsky and Freedberg[29] postulated the occurrence of a separate clinical syndrome of non-myxedematous hypometabolism based on long-term observations in 4 patients whose abnormally low BMR's, previously shown to be unresponsive to thyroxine, rose to normal levels on combined treatment of T-3 and thyroxine or high doses of T-3 alone. The above-mentioned authors suggested the theory that the hypometabolism in such patients was possibly on the basis of their failure to metabolize thyroxine to triiodothyronine at the cellular level. The original study by Kurland, Hamolsky and Freedberg[29]) was subsequently followed by several reports (Fields[12], Frawley *et al.*[14], Kupperman and Epstein[27], Levin[35], Morton[40], Tittle[52], Weidenhamer[53]) and editorials[4,24] confirming or refuting the existence of non-myxedematous or euthyroid hypometabolism, the sum total of which settled neither the myth nor reality of the syndrome, but tended to compromise on the rarity of its occurrence. Despite the preponderance of endocrinologists stating that they were still searching for their first bona fide case of euthyroid hypometabolism, or disparaging the entire matter as a commercial invention of the pharmaceutical houses, the controversy was kept alive by the enthusiasm of general practitioners who seemed to be getting favorable results with T-3 in several of their chronically tired, thyroid-resistant cases, and the gynecologists and urologists struggling with their infertility problems.

As a military physician dealing with a fair number of both tense, tired patients and infertile couples, and with the belief that such features of military medicine as free laboratory facilities and efficient patient follow-up were

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advantageous to clinical research, a careful search for hypometabolic patients was begun in the winter of 1957. The following report is a summary of two years' observations and collected data on 32 patients believed to represent cases of euthyroid hypometabolism.

Materials and Methods. Approximately 500 patients, military personnel and their dependents, were evaluated by the methods to be described. Among this group, 32 patients (6.4%) were found to meet the diagnostic criteria for euthyroid hypometabolism listed in Table 1. The age of patients ranged from 15 to 45 years with an approximate sex ratio of 2:1: 20 females, 12 males. The period of clinical observation and treatment ranged from 5 to 19 months and averaged 10.5 months per patient, with an average of 15 clinical appointments during this period. The endocrine evaluation of these cases consisted of the following diagnostic procedures: 1) A detailed history and physical examination, including the completion of a questionnaire listing 52 symptoms known to be associated with the protean hypothyroid state. 2) Baseline protein-bound iodine determinations (PBI); the normal range for our laboratory being 4.0 to 8.0 μg. 3) A second PBI drawn 24 hours after the intramuscular injection of ten international units of a potent thyrotropic hormone preparation* (TSH): (a rise in PBI above 1.5 μg. following TSH was interpreted as evidence of normal thyroid (thyroxine) function; a rise less than 1.0 μg. post-TSH, to represent true hypothyroidism). 4) Serial serum cholesterol determinations before and after treatment with placebo, thyroid and T-3 (normal range: 150 to 250 mg.). 5) Serial BMR's done under oral barbiturate pre-medication (Hortling and Hiisi-Brummer[21]) (normal range: plus 10% to minus 10%). 6) The electrometric recording of the Achilles tendon reflex by the Lawson kinemometer, done during each clinic visit (normal range: 150 to 240 milliseconds). Radio-iodine$_{131}$ uptakes were not done except to clarify a particular problem, such as, a PBI response which fell within the borderline range of a 1.0 to 1.5 μg. rise post-TSH.

Patients demonstrating both a normal baseline PBI and PBI-TSH response and a normal kinemometer tracing were excluded from this study. Patients believed to be cases of primary hypothyroidism as shown by an initial PBI below 4.0 μg. or a failure of the PBI to rise above 1.0 μg. post-TSH, or both, were likewise excluded from the hypometabolic group. The 32 patients displaying the combination of a normal TSH response in PBI and a prolonged (pseudomyotonic) tendon reflex tracing were then further investigated by serial BMRs, cholesterols, and kinemometer tracings while on the following medication given in sequence: a) a 4-week course of placebo therapy; b) a 4 to 8 week trial on desiccated thyroid, beginning with 120 mg. and increasing the dosage at 2-week intervals until either a 300 mg. level or thyroid intolerance was reached; c) finally, after thyroid had been discontinued for 10 days, a course of T-3 given in initial doses of 50 to 75 μg. per day and average maintenance doses of 75 to 150 μg. per day.

TABLE 1.—DIAGNOSTIC CRITERIA FOR EUTHYROID HYPOMETABOLISM

1. Symptom complex suggesting hypothyroidism and psychoneurosis.
2. Presumably normal thyroid (thyroxine) function as shown by a normal PBI and a normal rise in PBI post-TSH.
3. Objective evidence of deficient end-organ metabolism as shown by a low BMR and prolonged electrometric recording of the Achilles tendon reflex.
4. No response to placebo; equivocal or untoward response to desiccated thyroid in doses up to 300 mg. per day or toxicity.
5. A favorable response, both objectively and subjectively, to long term treatment with proper amounts of L-triiodothyronine.

Results. Among approximately 500 patients screened, 32 cases of euthyroid hypometabolism were diagnosed; a percentage incidence of 6.4%. However, since a sizeable number of the psychoneurotic and suspected endocrine cases were referred to this clinic for study by the Area's physicians, this percentage incidence cannot be said to reflect the occurrence of euthyroid

*Thyréostimuline, generously supplied by the Endopancrine Labs., Paris, France.

hypometabolism in the population at large. Table 3 lists the baseline results and changes secondary to treatment of the various thyroid-metabolic parameters employed in this study.

DIAGNOSTIC CRITERIA OF EUTHYROID HYPOMETABOLISM. 1) *A symptom complex and clinical appearance suggesting hypothyroidism in certain respects and psychoneurosis in others.* Table 2 compares the ten commonest complaints of a group of 104 hypothyroid patients versus the 32 hypometabolic patients in this series as compiled by the returns of a questionnaire listing 52 symptoms known to occur in hypothyroidism, but, likewise, common to psychoneurosis. A feature shared by both groups was the multiplicity of complaints with fatigue, lethargy, gonadal dysfunction, and nervousness predominating. Certain differences in the

TABLE 2.—THE 10 MOST COMMON SYMPTOMS REPORTED BY A GROUP OF 104 HYPOTHYROID PATIENTS COMPARED WITH 32 EUTHYROID HYPOMETABOLIC PATIENTS.

Hypothyroid			*Euthyroid Hypometabolic*		
Symptom	*Severe* (3,4)*	*Total* (1–4)	*Symptom*	*Severe* (3,4)	*Total* (1–4)
1. Fatigue-			1. Fatigue-		
worse in a.m.	25%	56%	worse in a.m.	43%	84%
worse in p.m.	66%	80%	worse in p.m.	24%	66%
2. Lethargy	45%	92%	2. Irritability & Mood Swings.	42%	87%
3. Irritability & Mood Swings.	42%	94%	3. Lethargy	38%	81%
4. Pre-menstrual Tension	40%	81%	4. Decreased Libido	30%	67%
5. Myalgias & Arthralgias	37%	78%	5. Pre-menstrual Tension	28%	80%
6. Irregular Menses.	37%	72%	6. Gastro-intestinal Complaints.	26%	65%
7. Cold Intolerance	33%	88%	7. Seborrhea or Hair Loss.	20%	55%
8. Dry Skin	32%	80%	8. Palpitations	18%	45%
9. Paresthesias.	28%	86%	9. Myalgias & Arthralgias.	15%	50%
10. Brittle, Splitting Hair or Hair Loss.	23%	70%	10. Shortness of Breath.	12%	44%

*Symptoms were graded according to severity on an ascending scale of 1 (mildly troublesome) through 4 (chief complaint).

TABLE 3.—PRE- AND POST-TREATMENT LABORATORY RESULTS IN 32 EUTHYROID HYPOMETABOLIC PATIENTS

		Average values and range					
Therapy	*N**	*None*	*N*	*Placebo*	*N*	*Thyroid*	*N*	*T-3*
PBI (μg.)	35	5.4 (4.2–7.7)		—		—		—
PBI rise post TSH	32	2.7 (1.6–4.0)		—		—		—
BMR	41	−15% (−33%–+7%)	32	−17.5% (−37%–+5%)	35	−13% (−33%–+11%)	104	−5% (−14%–+18%)
S-D Interval Kinemometer (millisec.)	44	255 (240–290)	64	255 (230–290)	134	250 (230–300)	258	200 (170–240)
Serum Cholesterol	32	225 (080–350)	18	233 (160–370)	23	220 (165–360)	34	215 (140–345)

*N = number of determinations

symptomatology of the hypometabolic patient when compared to the hypothyroid patient were, however, apparent, such as: fatigue worse at the beginning of the day rather than in the late afternoon or evening; oligomenorrhea, rather than met-menorrhagia; an oily, seborrheic condition of the skin and scalp rather than thick, dry skin; hypotension (oftentimes postural) instead of the tendency for hypertension reported as common in hypothyroidism (Sheedy and Lienhard[47]); normal or excessive sweating, rather than decreased sweating.

Pre-treatment measurement of body weight fell within the accepted range of normal in less than half of the hypometabolic group: 14 of 32 patients being 20% or more overweight, and 4 being 20% underweight. Two of the underweight patients were, in fact, suspected initially of being hyperthyroid until the report of their BMRs, both below minus 20%, necessitated a hasty reversal of opinion.

Findings on physical examinations were unremarkable, with the exception of eliciting the "hung-up" Achilles reflex *clinically* in several patients. Thyroid enlargement beyond slight fullness to the isthmus or thyroid nodules was distinctly uncommon, each abnormality being found only once in this series of cases.

2) *Presumably normal thyroid (thyroxine) function as shown by normal baseline PBIs and a significant rise in PBI post-TSH.* Although the TSH test as employed by Jeffries *et al.* in the diagnosis of equivocal hypothyroidism[22] and low thyroid reserve[23] employs both the radio-idoine$_{131}$ uptake and PBI response to TSH, the I_{131} uptake was omitted here of necessity. The response of the PBI alone to TSH is, however, believed to be a valid measure of thyroid responsiveness and thyroid reserve for the following reasons: a) the ability of the gland to respond to exogenous thyrotropin by the formation and release of active hormone (measured in the serum as PBI) is logically a more accurate test of thyroid potential than is the measurement of the gland's avidity for iodine. b) According to Levy[36], the experience of Jeffries' group with over 1,000 TSH tests, and our own experience with 200 or more tests using the PBI alone[15], clearly shows that the patient whose PBI rises 1.5 μg. or more following TSH is rarely hypothyroid at that time; in contrast, the patient whose PBI fails to rise above 1.0 μg. post-TSH usually responds to thyroid hormone replacement, both objectively (BMR, PBI, cholesterol, and others), and subjectively, and such improvement is maintained on physiological dosages. c) Among 70 patients found to have a normal PBI, and yet, a prolonged kinemometer tracing and low BMR, an adequate PBI-TSH response was seen in only 32 patients (the ones considered here to be euthyroid hypometabolic); the remaining 38 patients were later proved to be unequivocally hypothyroid, the false normal PBIs being secondary to iodine contamination from medications containing iodine or Roentgen-ray contrast media. Twenty-two of these 38 patients originally started on T-3 in view of the possibility that they might be hypometabolic rather than hypothyroid, later responded to equivalent amounts of desiccated thyroid regardless of a suggestive history or initial response. It is worth emphasizing that *the inadequate PBI response to a TSH preparation of known potency has reduced considerably the number of patients whose initial PBIs were reported as normal or borderline low and who might therefore have been included in the hypometabolic category.*

3) *Objective evidence of deficient end-organ metabolism as shown by*

BMR and electrometric recording of the ankle reflex. Although the electrometric recording of the abnormal tendon response in myxedema patients was first reported in the literature by Lambert in 1951[31], the simplicity and economy of the Lawson kinemometer makes it a utilitarian device for use in the clinic. Previous reports by Lawson have demonstrated the kinemometer to be 94% accurate in distinguishing between euthyroidism and even the milder degrees of hypothyroidism in over 3,000 patients tested (Lawson[33,34]). The fact that the standard BMR procedure requires complete relaxation on the part of the patient coupled with the fact that the typical hypometabolic patient is a tense, anxious individual, oftentimes leads to a false elevation of the BMR, particularly if it is the patient's first experience with the BMR procedure. In contrast, the contraction phase (*S-D interval*) of the Achilles reflex prolonged beyond the upper limits of normal of 240 milliseconds has been a constant finding in this series of 32 euthyroid hypometabolic cases, and is considered to be the most reliable criterion in screening such patients.

The *initial* BMR values in these 32 cases fell within the following ranges:

−35% to −20%, 12 patients
−20% to −10%, 5 patients
−10% to 0%, 13 patients
0% to +10%, 2 patients

Thus, it can be seen that little more than half of this group displayed low BMRs on initial testing. Subsequent BMRs in the remaining 15 patients, usually run on 2 or more consecutive mornings, revealed at least one BMR of −10% or below in all cases. A tabulation of BMRs and kinemometer tracings recording on 3 consecutive days in 10 "hypometabolic" patients is presented in Table 4. The superior accuracy of the kinemometer tracing in comparison to the BMR in the screening of patients for hypometabolism is evident, for although the S-D *interval* of the reflex varied less than 10 milliseconds, the BMR in 7 out of the 10 patients dropped significantly on each succeeding day. Elevated serum cholesterols were found in 8 (25%) patients, and responded significantly to T-3 therapy in 7 of the 8 patients.

That the contraction phase of the reflex is prolonged in both hypothyroid-

TABLE 4.—A COMPARISON OF BMRs AND KINEMOMETER TRACINGS RECORDED ON 3 CONSECUTIVE DAYS ON 10 EUTHYROID HYPOMETABOLIC PATIENTS.

	BMR (normal −10% to +10%)				*Kinemometer (normal 150–240 millisec.)*				
Patient	*Day 1.*	*2.*	*3.*	*Change*	*Day*	*1.*	*2.*	*3.*	*Change.*
K.K.	−6	−24	−22	−18%		250	250	250	0 millisec.
A.Mc.	−19	−21	−23	−4%		260	250	260	0 "
B.G.	+4	−5	−12	−16%		260	260	270	10 "
H.K.	−15	−14	−18	−3%		80	280	280	0 "
C.C.	−8	−19	−26	−18%		50	240	250	0 "
H.M.	−3	−18	−19	−16%		60	260	260	0 "
L.G.	−22	−25	−24	−2%		80	280	280	0 "
I.G.	+12	−1	−14	−26%		70	260	260	10 "
J.K.	−10	−15	−17	−7%		40	250	250	10 "

ism and euthyroid hypometabolism, suggests that the reactivity of the reflex best correlates with the peripheral or end-organ action of the thyroid hormones rather than the release of active hormone by the gland itself. The reflex tracing is thus similar to BMR and cholesterol, with the added advantage of being unaffected by emotional stimuli which might alter the BMR, or systemic factors, such as hepatic or biliary diseases which might influence the total cholesterol.

4. *No response to placebo; equivocal or untoward response to desiccated thyroid given in doses up to 300 mg. per day or intolerance.* Upon completion of the initial clinical and laboratory studies, all patients in this series were given a 4-week trial on placebo therapy. This procedure was followed in lieu of a double blind investigation because of the fact that the kinemometer tracing, repeated each clinic visit, would readily reveal (through changes in the baseline *S-D interval*) which patients were receiving active hormone medication. That the overall response of the hypometabolic patient to placebos was poor, was not surprising in view of the fact that these patients had previously been treated with numerous symptomatic drugs. At least two-thirds of this group had been taking, or were currently taking, one or more of the various tranquilizers. Weaning these patients off both tranquilizers and amphetamines proved difficult, but essential, as it is suspected that certain tranquilizer agents inhibit the action of exogenous T-3.

Following placebos, patients were started on 120 mg. of desiccated thyroid and the dosage increased by increments of 60 mg. at 2-week intervals until either objective improvement or symptoms of overdosage resulted. It was a curious finding that less than half, or 15, of the 32 euthyroid hypometabolic patients could tolerate more than 120 mg. of whole thyroid without toxicity despite the fact that they later proved to be able to tolerate equivalent amounts or more of T-3*. Only 4 patients reached the 300 mg. level without intolerance. Among 10 patients showing an initial response to thyroid with symptomatic improvement and rise in BMR, such improvement was short-lived: both symptoms and BMR returning to pre-treatment states within 3 to 5 weeks, despite continuance of thyroid medication.

5) *A favorable response, objectively and subjectively, to long-term treatment with adequate amounts of T-3.* The criteria used to judge unequivocal improvement on T-3 were the following: a) alleviation of clinical signs and symptoms secondary to hypometabolism, such as: nervousness, fatigue, genital dysfunction, and the like; b) return to within normal limits of the kinemometer tracing when the proper daily maintenance level of T-3 was reached; c) elevation of BMR to within normal limits, and *maintenance of a normal BMR over a minimum follow-up period of 5 months.*

The above objectives were reached in these cases with an average daily dose of 112 μg. T-3 and a dosage range of 75 to 150 μg. Patients were followed at bi-weekly intervals and T-3 dosages adjusted according to the S-D interval of the kinemometer, the optimum being a contraction phase approximating 200 milliseconds. A noteworthy difference was observed in the response of the hypothyroid patient versus the hypometabolic patient to initial treatment with 75 μg. T-3, in that the average hypothyroid patient improved rapidly, within 2 to 5 days, while the hypometabolic patient required 2 to 4 weeks and oftentimes, a higher dos-

*Dosage equivalents used in this series: 60 mg. thyroid = 37 μg. T-3.

age of T-3 before either symptomatic improvement or shortening of the S-D interval was noted. A time lag between the onset of T-3 therapy and its effect in raising the low BMRs in euthyroid hypometabolic patients has likewise been noted by Kurland[28], but remains unexplained.

The importance of weaning hypometabolic patients from tranquilizer drugs before instituting T-3 therapy, and the necessity of insuring that the patient receives adequate amounts of T-3, are illustrated in the following 2 case histories of patients outside this present series.

Case Reports. CASE 1. Mrs. L., a 42-year-old white woman, was referred to the endocrine clinic because of severe depression and myxedemous facial appearance. Symptoms of depressive reaction and generalized apathy had progressed during the previous 4 years despite long-term psychotherapy and electroshock treatment on one occasion. During her initial interview, Mrs. L. admitted taking tranquilizers and sedatives, but stated that she took them only sporadically.

The following laboratory data indicated euthyroid hypometabolism: Initial PBI, 4.0 μg.; PBI post-TSH, 8.0 μg.; BMR, minus 37%; cholesterol, 300 mg.; S-D interval, 280 millisec.

The patient was started on 75 μg. daily of T-3 and raised to 100 μg. within one week. Over the next 3 weeks, the dosage of T-3 was raised to 175 μg. per day without noticeable improvement. Repeat laboratory tests while patient continued on 175 μg. were essentially unchanged: BMR, minus 33; cholesterol, 320 mg.; and S-D interval, 270 millisec. Puzzled by the apparent lack of response, the patient's use of tranquilizers was elicited in more detail. This revealed that she was actually taking seven or eight 500 mg. Placidyl (ethchlorvynol) tablets per day in addition to three or four 25 mg. chlorpromazine tablets. Within 3 days after discontinuing tranquilizers completely, the patient now stated that she looked and felt better than she had in years. Her S-D interval was now 200 millisec. and a repeat cholesterol, 190 mg. The daily dosage of 175 μg. T-3 was continued until 48 hours later, at which time the patient complained of restlessness, tremor, excessive sweating, palpitations, and other symptoms of T-3 overdosage. Her S-D interval was now 140 millisec. In view of her previous resistance to T-3 while on tranquilizers, the patient was given 2.5 mg. of intramuscular reserpine and carefully observed. Approximately 8 hours later, the patient's hypermetabolic symptoms had abated, her pulse rate had decreased from 120 to 90 beats per minute, and her S-D interval had lengthened to 180 millisec.

Patient was subsequently regulated on 125 μg. T-3 daily and has done remarkably well.

COMMENT. The relationship between thyroid function and the action of certain tranquilizer agents, reserpine in particular, has now been the subject of several reports (Canary *et al.*[6], De Felice[8], DeFelice, Smith and Dearborn[9], Goodman[16], Kuschke and Gruner[30], Mayer, Kelly and Morton[37]). Both the observations of Canary[6] in human patients with thyrotoxicosis and DeFelice in rats[8], suggest that reserpine's amelioration of the hypermetabolism brought about by excess circulating thyroid hormones may conceivably involve inhibition of peripheral utilization of thyroid hormones, possibly by blocking the potentiating effects of the adrenal medullary hormones (Brewster *et al.*[5]). Since the initial experience with Mrs. L., parenteral reserpine has been successfully employed in 3 other patients who were inadvertantly overdosed with T-3, with both pulse rates and kinemometer tracings returning to normal in a matter of hours. It would thus appear that parenteral reserpine is an effective means to "back-titrate" the occasional patient, particularly the cardiac patient, made hypermetabolic by exogenous thyroid hormones.

CASE 2. Colonel H., a 35-year-old white man, was referred for endocrine evaluation of impotency of one year's duration. Other symptoms included: hair loss, morning fatigue, nervousness and feelings of inadequacy, lethargy and chest-wall myalgias. Laboratory data was reported as follows: Initial PBI, 5.2 μg.; PBI post-TSH, 7.5 μg.; BMR, minus 15%; cholesterol, 240 mg.; S-D interval, 250 millisec. Patient was started on 50 μg. T-3

daily, and instructed to return to the clinic in one week. He was unable to keep this appointment and was next seen one month later, at which time he complained of increased nervousness, palpitations, muscle cramps, insomnia, constant fatigue and a general listlessness. A kinemometer tracing showed a lengthening of the S-D interval to 270 millisec., despite his taking 50 μg. of T-3 daily. BMR was now minus 24%.

T-3 therapy was increased to 75 μg. daily for one week and then to 100 μg. The latter dosage was maintained for 2 weeks at which time the S-D interval shortened to 230 millisec., and then increased to 125 μg. per day. On this dosage the patient noticed considerable improvement in both his sexual performance and emotional stability. His S-D interval has stabilized at 200 millisec. and his BMR has ranged between minus 5% and zero over a 9-month period of follow-up.

COMMENT. A great practical advantage of the kinemometer over the standard BMR or PBI in following patients treated with thyroid hormones is that an estimate of metabolic status can be obtained while the patient is still in the doctor's office and thyroid medication adjusted without delay. Although initiating therapy with small increments of T-3 ranging from 12 to 25 μg. per day has been generally recommended by previous authors, a worsening of the patient's hypometabolic state in the early days of treatment with this regimen has been common enough and troublesome enough (as in the case of Colonel H.) that it is our preferred practice to start uncomplicated cases in the younger age groups on 75 μg daily and raise this to 100 μg. of T-3 within one to 2 weeks. The paradoxical worsening of the hypometabolic patient on the lower dosage schedules of T-3 has likewise been observed by Adelman[2]. Although a precise explanation for this phenomenon is not known, it is conceivable that T-3 in dosages of 12 to 60 μg. may profoundly suppress the endogenous production of thyroxine via inhibition of TSH release. Studies by Starr, Snipes and Liebhold-Schuek[50] and McConahey and Owen[39] have demonstrated marked suppression of RAI_{131} uptake in euthyroid individuals given small amounts of T-3, ranging from 8.8 to 35 μg. Thus treatment of a patient with 50 μg. T-3 daily (an amount which in itself is insufficient to maintain a normal BMR in an athyreotic individual), may conceivably, by inhibiting endogenous thyroxine release, make the patient more hypometabolic. Whether the mechanism by which T-3 suppresses TSH is more sensitive in the hypometabolic patient than in the normal is presently unknown, but the potency of T-3 in suppressing both TSH and RAI_{131} uptake is well established (Halmi *et al.*[19]). For this reason, T-3 therapy is logically given with the aim of either completely replacing endogenous thyroxine as the circulating thyroid hormone, or else, in dosages insufficient to suppress TSH, as reflected roughly in the radio-iodine uptake. Since the latter amount is variable and therefore difficult to approximate in any given case, the former procedure is the one that is recommended.

The use of T-3 in an investigative capacity in well over 200 patients has shown this substance to be remarkably free of untoward reactions. Aside from symptoms of overdosage, the only side effects noted were transient swelling of the salivary glands in 2 patients. The safety of T-3 when properly administered is in marked contrast to the reported incidence of sensitivity reactions to the various tranquilizer agents (Shaw and Felts[46]).

Discussion. The skepticism which has generally arisen over the alleged or actual existence of euthyroid hypometabolism is based on several reasonable objections. With the noteworthy exception of the original study by Kurland, Hamolsky and Freedberg,

based on carefully conducted long-term observations, the majority of case reports concerning euthyroid hypometabolism have lacked the support of convincing laboratory data. Despite the fact that almost all present-day techniques which measure the functional capacity of the thyroid gland itself are within normal limits in the hypometabolic patient, such tests are, nevertheless, necessary to separate cases of euthyroid hypometabolism from those of actual hypothyroidism. The BMR, which in theory should be significantly low, is oftentimes falsely elevated in the typically tense, anxious hypometabolic patient. The kinemometer offers the advantage of being consistent in value when repeated several times in the same patient (Lawson[33]). Double-blind studies alternating T-3, desiccated thyroid, and placebos, encounter the difficulty of using predetermined amounts of T-3 rather than dosages individually adjusted by objectively measured metabolic response. The dosages used in a double blind evaluation can be a crucial factor as was shown in the study carried out in Great Britain to determine the relative effectiveness of aspirin versus cortisone in the treatment of acute rheumatic fever (Robinson[42]). Likewise, the interpretation of a therapeutic trial based on subjective response alone is frought with error. Not only is a positive response to T-3 inconclusive evidence of hypometabolism rather than placebo effect, but a negative response does not rule out a true hypometabolic state improperly or inadequately treated. If a therapeutic trial does not extend beyond the time lag oftentimes seen in the hypometabolic patient before a response to T-3 is forthcoming, or if the patient is taking tranquilizers such as reserpine at the same time, results can be quite equivocal. Furthermore, in the absence of objective means by which to spot-check the patient's metabolic response, such as the BMR or kinemometer, the nervousness produced by emotional stress or pre-menstrual tension can easily be confused with T-3 overdosage.

During the past year, two reports have been published which utilized the double blind method in studying patients suspected of euthyroid hypometabolism; both of them, failing to confirm the existence of the syndrome by the methods employed. The first such investigation, by Levin[35], found no significant difference in the response to T-3, as compared to placebo and L-thyroxine, in 6 patients studied. A maximum dosage of 75 μg. of T-3 daily was prescribed and this was taken for a period of 2 weeks by 2 patients and 4 weeks by 4 patients; the study being concluded after a total period of 4 weeks on each of the three medications. However, since it has been our usual experience that the majority of hypometabolic patients usually require 2 to 3 weeks on 100 μg. or more of T-3 before either objective or subjective improvement is forthcoming, the failure of Levin's patients to show a positive response to this type of T-3 therapy is not unexpected.

A second study of suspected hypometabolic patients was reported by Sikkema[48], in which 20 patients with low BMRs (averaging —16%) and normal PBI values, showed no significant change in either symptoms or BMR when treated with placebos or triiodothyronine for a period of 6 weeks. The daily dosage of T-3 employed in individual cases is not stated, although the dosage range for the group was said to be from 62.5 to 150 μg. Among the patients responding favorably to T-3, an identical response was observed after T-3 therapy had been discontinued and the patients placed on an equivalent amount of desiccated thy-

roid. Sikkema further states that, among 73 patients considered by her to be hypothyroid, initial PBI determinations were carried out in only 28 cases; 21 of the 28 PBI values falling within the normal range. Based on this, Sikkema concludes that the BMR is superior to the PBI determination as a screening test for hypothyroidism.

This raises the objection that, since the PBI values reported by Sikkema's laboratory are normal in the majority of her hypothyroid patients as well as in the patients suspected of euthyroid hypometabolism, this diagnostic procedure cannot be justifiably employed to separate cases into euthyroid, hypothyroid or hypometabolic categories for the purpose of double-blind investigations. Patients with true hypothyroidism would naturally be expected to respond equally well to equivalent amounts of T-3 or whole thyroid. The question is thus raised as to whether or not the 20 patients suspected of being hypometabolic by Sikkema were actually hypothyroid. It was with this important distinction in mind that TSH tests were carried out on the 32 patients comprising this present study.

The theory originally proposed by several authors to account for the occurrence of euthyroid hypometabolism: namely, that such patients are unable to deiodinate thyroxine to T-3, its peripherally active metabolite, has not met with general acceptance. Based on preliminary data by Pitt-Rivers, Stanbury, and Rapp[41], the abovementioned theory seemed an attractive one, but rested on the premise that the conversion of thyroxine to T-3 was a natural pathway for the metabolism of the thyroid hormones. Neither Roche and Michel[44], working with *in vivo* systems, nor Lassiter and Stanbury[32], who attempted to reduplicate the original experiments of Pitt-Rivers *et al.*, could confirm the conversion of thyroxine to T-3 *in vivo*, although there is some documentation that *in vitro* slices of kidney, liver, heart and skeletal muscle are able to deiodinate small amounts of thyroxine to T-3 (Albright and Larson[3]). The radio-active labeled T-3 recovered in the plasma of humans and animals by various investigators (Roche and Michel[45], Starr, Snipes and Liebhold-Schuek[50]) is believed to be formed and released directly from the thyroid gland itself.

The failure to find abnormalities in either the thyroidal iodine trap, the formation and release of thyroxine, binding mechanisms which transport thyroid hormones through the plasma, or the TSH response, raises the possibility that the pathophysiology underlying the hypometabolic state may involve neuro-endocrine systems outside the thyroid gland itself; that thyroid function is only secondarily affected, as in hypopituitary myxedema, resulting in an inhibition of the formation and release of T-3, or else, an exhaustion of thyroidal stores of T-3. In short, rather than being a thyroid disease at all, euthyroid hypometabolism may conceivably be a state of T-3 deficiency secondary to dysfunction at the corticohypothalmic level.

From the experimental studies of Greer[17], Harris and Woods[20] and many others (D'Angelo[7], Yamada and Greer[54]), the hypothalamus is known to exert a regulating influence on many phases of thyroid-pituitary function; an intact hypothalamus being essential to the proper elaboration of the thyroid hormones. Clinically, the typical hypometabolic patient bears close resemblance to the cases categorized by Starr as hypothalmic hypothyroidism several years ago[49]. The following evidence can be cited to suggest relative gonadal failure: amenorrhea or oligomenorrhea (in contrast to the metmenorrhagia usually encountered in

the hypothyroid female), anovulation and infertility, occasional uterine hypoplasia, impotency or frigidity, low or low normal sperm counts with depressed sperm motility, and the like.

Implicating mild adrenal dysfunction, one finds: easy fatiguability, postural hypotension, functional hypoglycemia and, on occasion, low urinary 17-ketosteroids. To date, three hypometabolic women have been found to have total urinary 17-ketosteroids below 3 mg. per 24 hours; the presenting complaints in 2 of the 3 being infertility. A significant rise in 17-ketosteroids to levels of 6.6, 7.3 and 9.1 mg. per 24 hours was observed in these 3 patients consequent to T-3 therapy. An investigation of 17-hydroxycorticoid excretion in 7 hypometabolic patients revealed normal values throughout. Kupperman and Epstein[27] have reported flat oral glucose tolerance tests to be a frequent finding in euthyroid hypometabolic patients. Although not carried out as a routine, glucose tolerance tests were performed in 9 patients in this series and judged to be flat in 4.

In both mannerisms and appearance, the hypometabolic patient bears an almost indistinguishable resemblance to the true psychoneurotic; the clinical distinction being possible only by the presence of an abnormal Achilles reflex tracing. That such a distinction is worth making at all, is upheld by the overall improvement observed by this author in the great majority of euthyroid hypometabolic cases when treated with T-3. In contrast to this, stands the fate of the true neurotic: dependence on tranquilizers or expensive, prolonged psycho-therapy.

An important aspect of the relationship between euthyroid hypometabolism and psychodynamic symptoms and one which remains as yet undecided, concerns the sequence of their dual occurrence: namely, does the hypometabolic state precede the overt neurosis, or rather, does the psychodynamics of the neurosis itself disturb neuro-endocrine function sufficiently to lead to T-3 deficiency and euthyroid hypometabolism? An intriguing study by Kissin *et al.*[26] attempted to show the presence of parasympathetic overactivity and mild pan-endocrine hypofunction in a series of 19 patients with "psychic fatigue"—usually severe anxiety states or depressive reactions; 65% of which, likewise, had low BMRs. Without venturing into a discussion of cause-and-effect mechanisms, Kissin's study suggested that the concomitant presence of panendocrine hypofunction and severe psychoneurosis is not uncommon when endocrine studies are pursued in such patients.

Though it has been long known that epinephrine potentiates the metabolic response of thyroid hormones at the peripheral level (Ellis[10]), recent experiments by Ackerman and Arons[1] suggest a direct effect of epinephrine and norepinephrine on the acute release of thyroxine and triiodothyronine by the thyroid gland. Radio-chromatographic results in two experiments were particularly interesting in that they demonstrated release of both labeled thyroxine and T-3 following epinephrine administration, but release of thyroxine alone following TSH. The possibility is raised by these authors that the thyroid may play a much more significant role in the stress reaction than was previously realized, and that the adrenal medullary hormones released during stress may, in turn, stimulate the thyroid's release of T-3 and thyroxine. If, in the future, it can be shown that T-3 is preferentially released by the thyroid during stress, particularly emotional stress, then it is conceivable that hypometabolism could result from a stress depletion of T-3 reserves, rather than an actual inhibition of T-3 release.

The following case history of a pa-

tient with anorexia nervosa is cited as a possible example of cortico-hypothalmic depression of basal metabolism reversible by therapy with T-3:

Case Report. Mrs. C.S., a 30-year-old white woman, was first seen in mid-July, 1958, following hospitalization for what appeared to be a classical picture of anorexia nervosa. The patient first experienced the gradual onset of fatigue and apathy following the uncomplicated pregnancy and birth of her first child in March, 1958. A BMR taken in early June was minus 25%. The patient's weight at that time was 130 lbs., her normal weight. Her PBI was reported as 5.5 μg. The patient was started on 120 mg. desiccated thyroid by her physician and was being maintained on 180 mg. per day when she progressed to full-blown anorexia nervosa. When hospitalized in July, her body weight had decreased to 98 lbs. and her BMR was then minus 33%. Increasing the thyroid to 300 mg. per day, although raising her PBI to 8.2 μg., had only slight effect on her BMR, raising it to minus 30%. Additional endocrine studies showed a low level of urinary gonadotropins, decreased cornification on vaginal smear, normal ACTH response of 17 keto- and hydroxycorticoids, and a normal TSH response: the PBI rising from 7.8 to 10.4 μg. post-TSH.

In early August, after thyroid medication had been withdrawn for 10 days, the patient was started on 75 μg. T-3 daily. One week later, while on 100 μg. T-3, her BMR had risen to minus 20%. T-3 therapy was subsequently raised to 150 μg. per day and maintained at that dosage for 2 months, the BMR varying from minus 14% to minus 3%. Concomitant with the rise in BMR, the patient became more responsive to psychotherapy. At the time of her hospital discharge in September, 1958, her weight had increased to 120 lbs. and she seemed capable of returning to full-time duty as a housewife. She is presently being maintained on 125 μg. T-3 and her BMR has remained above minus 10 on repeated testings.

COMMENT. Although anorexia nervosa is generally considered to be basically a non-endocrine disorder, two relatively constant findings have been low urinary gonadotropins and low BMRs (Emanuel[11]). The latter is inconsistently affected by physiological amounts of whole thyroid and usually attributed to malnutrition. In the case of C.S., however, a BMR of minus 25% was documented several weeks prior to any significant weight loss. Furthermore, her low BMR, unaffected as it was by 180 to 300 mg. of desiccated thyroid, responded promptly to T-3 and was maintained within normal limits, thereafter. Whether the abovementioned case represents an actual instance of hypothalmic suppression of both gonadotropin and metabolic (T-3) function, with thyroid (thyroxine) and adrenal function being spared, or whether, in fact, T-3 deficiency is typical for anorexia nervosa cases in general, is certainly debatable. A second anorexia patient treated in a nearby hospital with T-3 and a case reported by Flack[13] seemed to respond in similar fashion, although the full details on these patients are lacking.

Conclusions. On the basis of long-term observations made on the 32 cases comprising this report, the syndrome of euthyroid hypometabolism is believed to exist as a distinct clinical entity, although its etiology and true incidence among the population at large remains undetermined. Such patients are oftentimes mistaken for psychoneurotics and are thus analyzed, tranquilized or merely despised, with haphazard results. Treatment of such cases with T-3 is not always a cure-unto-itself, however, for a neurosis which either antedated the hypometabolic state or became rooted in it is not likely to respond as quickly as a low basal metabolism. T-3 is, nevertheless, proper and effective supportive therapy and may further the ultimate response of the hypometabolic patient to needed psychotherapy. Several factors believed to have influenced and perhaps concentrated the present series of cases are worth reiterating. The hypometabolic patient, with his multiplicity of complaints, is prone to congregate

wherever free medical care is offered, such as at an Army medical dispensary. It is highly likely that such patients will be channeled towards the psychiatric rather than endocrine clinic unless, as was the case during the first year of this study, no psychiatric treatment facilities are available. The psychiatric outpatient clinic is thus recommended as being fertile ground for the endocrinologist seeking cases of euthyroid hypometabolism. As a corollary: patients referred for psychiatric aid can and should be easily screened for hypothyroidism or hypometabolism by the kinemometer. An S-D interval prolonged beyond normal limits is an objective finding uninfluenced by doctor-patient relationship or the power of suggestion, and obviates, to a great extent, the necessity of performing double-blind studies. As a parameter of metabolic status and response to thyroid medication, the kinemometer has proved superior to the conventional BMR. Since no one has yet improvised a laboratory test to establish a positive diagnosis of psychoneurosis, the kinemometer tracing can, at least, separate the psychoneurotics with normal thyroid-metabolic function from the neurotics or non-neurotics with concomitant hypometabolism. The overall response of the euthyroid hypometabolic cases to optimum doses of T-3 as *sole* medical treatment was impressive and sufficient to render the patient relatively asymptomatic in 23 of 32 cases. The remaining 9 patients showed physical improvement, but required short-term psychotherapy to help them cope with their everyday emotional problems.

Finally, it is the author's belief that the favorable results brought about by T-3 therapy in these patients was not a placebo-type response. Insofar as possible, objective, and not subjective, criteria were used to judge improvement; the primary goals being a normal reflex pattern and BMR, rather than alleviation of particular symptoms. Since Lawson has convincingly shown that the kinemometer is affected only rarely by medical conditions other than hypothyroidism or hypometabolism (Lawson[33]), and very few drugs outside of the thyroid hormone, it is deemed unlikely that the changes noted in the S-D interval during T-3 therapy resulted from anything other than a raised metabolism. Lastly, considering that the majority of these patients had taken various symptomatic medications in the past, were, in fact, inveterate pill-takers, and that these patients were informed that they would probably require lifetime maintenance on T-3 therapy, it is believed unlikely that their general improvement was artifactious.

Summary. Among approximately 500 patients screened for the controversial syndrome of euthyroid hypometabolism, 32 individuals (6.4%) were found who met the five diagnostic criteria for this disorder proposed by the author. Such patients showed normal PBI values and a normal rise in PBI after TSH, and yet, BMRs and kinemometer tracings of the Achilles reflex in the hypothyroid-hypometabolic range. Although unresponsive to placebos or desiccated thyroid, such patients responded favorably, both objectively and subjectively, to therapy with L-triiodothyronine. Dosages of L-triiodothyronine ranged from 75 to 150 μg. per day and averaged 112 μg. per patient. A paradoxical worsening of hypometabolic symptoms when patients were given insufficient amounts of L-triiodothyronine, and the necessity of weaning such patients off tranquilizers prior to initiating therapy is discussed. Although the true etiology and incidence of euthyroid hypometab-

olism remain undetermined, it is believed that this syndrome does, in all likelihood, exist, and should be looked for, particularly in patients whose complaints suggest either hypothyroidism or psychoneurosis.

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SUMMARIO IN INTERLINGUA

Le Caso pro Hypometabolismo Euthyroide

Inter approximativemente 500 patientes scrutinate pro le controverse syndrome de hypometabolismo euthyroide, 32 esseva trovate (6,4%) qui satisfaceva le cinque criterios diagnostic pro le mentionate disordine proponite per le presente autor. Tal patientes monstrava normal valores de iodo ligate a proteina e un normal augmento del iodo ligate a proteina post administrationes de hormon thyroido-stimulante sed, nonobstante, valores pro le metabolismo basal e registrationes cinemometric del reflexo de Achilles in le ordine hypothyroido-hypometabolic. Ben que non responsive a placebos o a desiccate extractos thyroide, tal patientes respondeva favorabilemente—secundo criterios subjective e objective —al therapia con L-triiodothyronina. Le dosage de L-triiodothyronina variava inter 75 e 150 μg per die, con un valor medie de 112 μg per patiente. Un pejoration paradoxe del symptomas hypometabolic quando le patientes recipeva insufficiente quantitates de L-triiodothyronina esseva notate. Iste phenomeno es discutite e etiam le necessitate de dishabituar tal patientes ab le uso de tranquillisatores ante le initiation del therapia a L-triiodothyronina. Ben que le ver etiologia e incidentia de hypometabolismo euthyroide remane indeterminate, le these es presentate que le existentia de iste syndrome es multo probabile e que su presentia deberea esser suspecte in patientes, super toto, con gravamines que suggere hypothyroidismo o psychoneurose.

PAINLESS CHRONIC PANCREATITIS, CHYLO-ASCITES, AND CHYLOTHORAX. REPORT OF A CASE

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Chylous ascites, especially of non-traumatic origin, is rare. Pratt and McCready[11] found only 10 cases of chylous ascites recorded in the English medical literature in a 15-year period. Chylous ascites as a complication of chronic relapsing pancreatitis has recently been reported for the first time (Gambill, Walters and Scanlon[7]).

Case Report. Mrs. M.D., a 76-year-old, white widow, registered at the Grand Forks Clinic on September 3, 1958. The patient's memory was impaired, but two of her daughters supplied historical details.

There were two chief complaints. The first was diabetes mellitus of more than 10 years' duration. The patient had been treated with daily small doses of insulin, but this medication was voluntarily discontinued one year before registration. Dietary management consisted of a self-styled, diabetic diet. Episodes of diabetic acidosis or insulin reaction were not recalled. The patient had never tested her urine for sugar. There was no familial diabetes mellitus.

The second complaint was persistent depression subsequent to the death of the patient's husband approximately one year prior to registration. A thorough review of systems revealed only that the patient had a chronic cough, productive of scant, clear, mucoid sputum and had smoked an average of less than one pack of cigarettes a day during the preceding 28 years.

Physical examination showed a white woman who appeared approximately her stated age, seemed sad, picked at her clothing, and wrung her hands continuously. Weight was 140 pounds; temperature, 98.6° F.; pulse rate, 80 a minute; respirations, 16 a minute; and blood pressure, 154 mm. Hg systolic and 96 mm. Hg diastolic. The optic fundi were hidden behind dense lenticular opacities. Over the lower lobe of the left lung there were palpable and audible, inspiratory and expiratory rhonchi and expiratory sibilant rales. The liver extended 6 cm. below the right costal margin in the midclavicular line and 4 cm. below the xiphoid process. Except for the absence of pulsations of both dorsalis pedis arteries, all major arterial pulses were strong. There was no pallanesthesia at the ankles. The remainder of the physical examination was essentially normal.

Laboratory Data: Hemoglobin was 17.1 gm.%; leukocyte count, 8,700 per c.mm.; and erythrocyte sedimentation rate, 6 mm. per hour (Westergren method). Urinalysis was normal. Fasting (true) blood sugar was 150 mg. per 100 ml; and blood urea nitrogen, 14.5 mg. per 100 ml. Postero-anterior chest roentgenogram demonstrated only calcium in the arch of the aorta.

The patient and her daughters were taught a qualitative, diabetic diet. Two days later, the patient's fasting (true) blood sugar was 153 mg. per 100 ml. Therapy with tolbutamide was then instituted. During the subsequent 10 days, weakness persisted; and the patient failed to eat well.

On October 14, 1958, the patient's weight was 129½ pounds; and her daughters complained that the patient still did not eat but would only sit and worry. The fasting (true) blood sugar was 150 mg. per 100 ml. Tolbutamide therapy was stopped.

On October 28, 1958, the daughters were concerned because of frequent, soft bowel movements; however, the patient would admit to only one or two defecations a day. There was no diarrhea during the night. A better appetite, increased interest in surroundings, and more physical activity were reported.

The patient did not return to the Grand Forks Clinic until January 13, 1959. Bowel movements were then reported as watery and frequent. The patient was awakening

early in the morning and was anorexic. Body weight was 114½ pounds. Emaciation and muscular weakness were quite evident. Fasting (true) blood sugar was 140 mg. per 100 ml.; and serum carotene, 140 I.U. %. The daughters requested a trial of brandy as an appetite stimulant; so brandy, methylphenidate hydrochloride, and Belladenal were prescribed.

On February 10, 1959, the patient was admitted to the Deaconess Hospital, Grand Forks, North Dakota, for further investigation. Body weight had declined to 105 pounds. A productive cough was present, but the lungs were free of rhonchi and rales. A sharp liver edge was palpated 8 cm. below the tip of the xiphoid process.

Total serum protein was 5.71 gm.%; serum albumin, 2.94 gm.%; and serum globulin 2.77 gm.%. Fasting (true) blood sugars were 116 and 117 mg. per 100 ml. It was not possible to collect feces for quantitative determination of fat and nitrogen. Roentgenologic examinations of the esophagus, stomach, entire small intestine, and colon revealed only diverticulosis of the colon. Scattered irregular areas of apparent calcification were noted throughout the abdomen; most appeared to be in vascular structures; some, in the spleen; and one, possibly in the gallbladder.

The patient ate practically nothing, smoked cigarettes incessantly, and was difficult to manage because of depression, indequate grasp of the situation, poor memory, and, at times, mental confusion. She was dismissed from the hospital on February 14, 1959, with the following medications: Siblin, propantheline bromide, methylphenidate hydrochloride, and Benylin Expectorant.

The patient was next seen at her home on April 21, 1959, because of gradual increase in size of her abdomen. Weight loss and frequent soft stools had been continuous. Her chief source of nourishment was eggnogs with brandy. On physical examination, there were sonorous and sibilant, expiratory rales, especially at bases of each lung. The abdomen was very protuberant, flanks were bulging and had a dull percussion note, and shifting dullness and a fluid wave were present. Rectal examination was negative. Slight, but significant, edema of the ankles and feet was present.

About noon on May 18, 1959, without assistance the patient got out of bed at home and fell. There was immediate pain in the right hip and inability to move the right lower extremity. The patient was admitted to the Deaconess Hospital, Grand Forks, North Dakota.

Temperature was 98.4° F.; pulse rate, 108 a minute; respirations, 26 a minute; and blood pressure, 118 mm. Hg systolic and 76 mm. Hg diastolic. The patient was extremely emaciated and had grunting expirations. The trachea was centered in the sternal notch. The posterior one-half of the left side of the chest (with the patient supine) had a flat percussion note and absent breath sounds. Expiratory rhonchi were audible over the upper one-half of the anterior aspect of the left side of the chest and over the lower one-half of the anterior and lateral aspects of the right side of the chest. The abdomen was more protuberant but otherwise as described on April 21, 1959. The right lower extremity was shortened and externally rotated. Palpation of the proximal part of the right thigh and any motion of the right thigh caused considerable pain.

Roentgenograms of the pelvis and chest were interpreted as fracture of the right femur in the intertrochanteric region and extensive left pleural effusion. An orthopedist instituted treatment of the fracture of the femur with Buck's traction.

Hemoglobin was 11.7 gm.%; white blood cell count, 7,000 per c mm.; and erythrocyte sedimentation rate, 46 mm. in one hour (Westergren). The urine had a specific gravity of 1.018, 1 plus albuminuria, trace of sugar, no diacetic acid, and a "packed field" of white blood cells on microscopic examination. Prothrombin time was 18 seconds (control: 15 seconds); direct serum bilirubin 0.2 mg. per 100 ml.; total serum bilirubin, 0.85 mg. per 100 ml.; alkaline phosphatase, 2.4 Shinowara-Jones-Reinhart units (normal: 2 to 9); total serum proteins, 5.9 gm.%; serum albumin, 2.54 gm.%; and serum globulin, 3.36 gm.%.

That afternoon the patient began to vomit. The vomitus was reported as projectile, contained red flecks, and was strongly positive for blood by the guaiac test.

The following morning, the patient was quite drowsy and had definite rigidity of her neck. A lumbar puncture was done. The cerebrospinal fluid pressure was 170 mm. of cerebrospinal fluid, and this fluid demonstrated no cells on microscopic examination. 35 mg. per 100 ml. of protein, trace of globulin by the Pandy test, flat colloidal gold curve, and non-reactive VDRL test for syphilis. Roentgenogram of the skull was normal.

Because of dyspnea, a left thoracentesis was performed on the third hospital day. Two thousand milliliters of milky-creamy (chylous) fluid were aspirated. This fluid con-

tained much fat when stained with Sudan IV, 690 mg. per 100 ml. of total lipids, 1,449 red blood cells and 102 white blood cells per c.mm., 5.5 gm.% of protein, no acid fast bacilli on direct smear or culture, and no neoplastic cells. The specific gravity of this chylous fluid was 1.010, and the opacity was partially clarified by extraction with ether.

The diabetes mellitus presented no problem. Ketone bodies were absent from the urine. Swallowing or expectorating oral and tracheobronchial secretions progressively became more difficult. Death occurred on the morning of May 22, 1959.

NECROPSY.* *Gross Examination*: The body was that of an emaciated, elderly woman with a markedly protuberant abdomen. The right lower extremity was externally rotated due to a fracture of the neck of the right femur. There was fluid in all body cavities: (1) Chylous—opaque, milky—fluid (6,000 ml. in the peritoneal cavity and 3,000 ml. in the left pleural cavity) and (2) clear, pale yellow fluid (700 ml. in the right pleural cavity and 150 ml. in the pericardial sac).

The most significant finding was a small fibrotic pancreas. The principal pancreatic duct had a diameter of 3 to 4 mm. in the tail of the pancreas and 4 to 8 mm. in the body and head of the gland. The interlobular ducts were also dilated.

Fibrosis was most evident in the area of the head of the pancreas, which was fixed to the posterior abdominal wall. Within the head of the pancreas, 2 cm. from the duodenum, the main pancreatic duct suddenly narrowed as it entered a dense, fibrous area but could, with difficulty, be traced to the duodenum. There was no ampulla of Vater, the common bile duct and the duct of Wirsung entered the duodenum separately. The accessory pancreatic duct was also very dilated and could easily be traced to its termination in the duodenum.

The dense fibrosis in the head of the pancreas extended posteriorly and involved the periaortic tissues about the origins of the celiac and superior mesenteric arteries, celiac ganglia, and adjacent portions of the right sympathetic chain. This fibrosis also involved and obstructed the lower part of the cisterna chyli and its tributary chyle radicals.

The upper part of the cisterna chyli was grossly normal. The thoracic duct was dissected and found to be slightly dilated, was neither fibrotic nor obstructed at any point, and terminated in three channels that separately entered the venous system at the junction of the left subclavian and internal jugular veins.

The wall of the gallbladder was thickened, fibrotic, and firmly contracted around a mass of calculi. One calculus was impacted in the neck of the gallbladder and obstructed the cystic duct. Beyond this point the cystic duct was normal. The common bile duct was normal in its entirety; it was not involved in the dense fibrosis in and around the head of the pancreas.

The liver was not enlarged. The cut surface of the liver revealed mottling and exaggeration of the hepatic markings, as seen in early chronic passive congestion.

Other significant findings were:

(1) Considerable mucoid exudate throughout the tracheobronchial tree; (2) fibrosis of the myocardium especially in the upper part of the interventricular septum and near the apex of the left ventricle; (3) much congestion of the gastric mucosa and a small amount of coffee-ground fluid in the stomach; (4) diverticulosis of the colon; (5) a relatively small spleen with fibrosis of the splenic pulp; (6) coarse and fine pitting of the surface of the kidneys and moderate thinning of the renal cortex; and (7) moderate cortical atrophy, some atrophy of the white matter, and moderate dilatation of the lateral ventricles of the brain.

Histologic Examination: Multiple sections from the pancreas showed dilatation of all ducts and ductules, dense interlobular and interacinar fibrosis, complete destruction of acini and islets of Langerhans in some areas, atrophy of acini with persistence of remnants of islets of Langerhans in other areas, and an exudate of scattered or grouped lymphocytes throughout the gland. In the head of the pancreas, at the site of the great narrowing of the duct of Wirsung, periductal fibrosis only was present.

The wall of the gallbladder was extremely fibrotic and hyalinized. Numerous Rokitansky-Aschoff sinuses containing small calculi were present. The histologic alterations of mild chronic passive congestion were evident in the liver. The right hepatic artery was occluded near its origin by an organized thrombus.

Mild congestion, edema, and pigmented macrophages were present in the lungs. The myocardium contained scattered areas of fibrosis and atrophic muscle fibers. Patchy loss of glomeruli and tubules was apparent

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in the kidney; the remaining glomeruli were normal. Multiple sections of the brain revealed mild, toxic degeneration of neurons, relatively acute and of nonspecific type, and perivascular areas of demyelinization.

COMMENT. Clinically the hallmark of chronic pancreatitis is recurrent bouts of severe upper abdominal pain (Gross[8]). However, the diagnosis of chronic pancreatitis usually depends upon the recognition and correct interpretation of one or more of the three sequelae of this disease. These sequelae are calcification of the pancreas, diabetes mellitus, and steatorrhea.

Pancreatitis apparently may be a painless disease (Evans[5], Evans, Gross and Baggenstoss[6], Gross[8], Gross, Comfort and Waugh[9]). Acute edematous pancreatitis, present at necropsy, was unaccompanied by pain in 15 of 25 cases (Evans[5], Evans, Gross and Baggenstoss[6]). It is conceivable that recurrent attacks of acute edematous, or even necrotic, pancreatitis could painlessly cause progressive fibrosis of the pancreas (Anglem and Lee[1], Peterson and Cole[10]).

Bartholomew and Comfort[2] recorded 10 cases of painless, or relatively painless, chronic relapsing pancreatitis. In 5 of their 10 cases, all three of the sequelae of chronic pancreatitis were present; in 3 of their 10 cases, the sequelae were calcification of the pancreas and steatorrhea; and, in the remaining 2 cases, the sequelae were diabetes mellitus and steatorrhea. Therefore, in only 2 of their 10 cases of chronic pancreatitis without pain there was no pancreatic calcification. All 10 of their patients experienced loss of weight in spite of ravenous appetities.

In the presently reported case, the diabetes mellitus and diarrhea were considered as possibly due to internal and external pancreatic insufficiency, respectively. The absence of calcification of the pancreas by roentgenographic study and the failure to demonstrate a low serum carotene (Wenger, Kirsner and Palmer[14]) resulted in the dismissal of chronic pancreatitis as the probable diagnosis.

Chylous ascites of non-traumatic origin is usually due to neoplastic or tuberculous obstruction or destruction of the thoracic duct, its tributaries, or its branches (Yater[16]). The presence of chylous ascites of non-traumatic origin almost invariably is indicative of a fatal disease.

Few cases of chylous ascites of non-traumatic origin have been due to reversible processes. Adhesive bands stretching across the root of the mesentery of the small intestine have obstructed the chyle radicals in the mesentery (Pratt and McCready[11], Quincke[12], Wyatt and Gross[15]). Lysis of these bands has reestablished the flow of chyle from the lacteals to the cisterna chyli and completely alleviated the chylous ascites (Pratt and McCready[11], Wyatt and Gross[15]).

Pseudocysts of the pancreas have also been associated with and presumably responsible for chylous ascites (Collins[3], Crandell *et al.*[4]). Surgical drainage of such cysts cured the chylous ascites evidently by relieving obstructive pressure on the cisterna chyli (Crandell, Stueck and McEvoy[4]).

Although chylous ascites may exist independently, it is generally found in association with chylothorax (Pratt and McCready[11]). The chylothorax may occur even though the cause of the chylous ascites is subdiaphragmatic. Apparently the chylous ascitic fluid traverses the diaphragm via lymphatic channels and enters the pleural space. Stewart and Linner[13] injected congo red dye intraperitoneally in a child with chylous ascites and right chylothorax. The dye stained the chylous pleural fluid.

The fibrosis of chronic pancreatitis has occluded the common bile duct. Peterson and Cole[10] reported 3 such occurrences; Anglem and Lee[1] reported one. Anglem and Lee's case was unusual, for the patient must have had two gallbladders—". . . cholecystectomy was done . . ." and four years later ". . . gallbladder was then removed. . . ."

In the present case, the fibrotic process in the pancreas involved the chyle radicals of the small intestine and the cisterna chyli. Such a process need occur only in the strategic area where the intestinal chyle radicals converge to run along the superior mesenteric artery towards the cisterna chyli. This is the area where the superior mesenteric artery comes from behind the body of the pancreas, crosses anterior to the uncinate process and the third portion of the duodenum, and enters the root of the mesentery of the small bowel.

The chylous ascites in the case recorded here was due to chronic relapsing pancreatitis and, therefore, irreversible. The chylothorax was due to transfer of the chylous fluid from the abdominal to the left pleural cavity through the lymphatic vessels of the diaphragm. The left chylothorax was not due to obstruction or rupture of the thoracic duct.

Summary. A case of painless chronic relapsing pancreatitis responsible for diabetes mellitus, probable steatorrhea, chylous ascites, and left chylothorax has been presented. The chylous ascites was due to obstruction of the chyle radicals of the mesentery of the small intestine and the cisterna chyli by the fibrotic process initiated by the pancreatitis. The chylothorax was due to transfer of the chylous fluid from the abdominal to the pleural cavity via the diaphragmatic lymph vessels. Chronic relapsing pancreatitis, therefore, is another non-neoplastic cause of the rare condition of chylous ascites.

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(Interlingua on page 530)

PROGRESS
OF
MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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PLASTIC SURGERY OF THE NOSE

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A REVIEW of progress in otolaryngologic plastic surgery reveals advances commensurate with those in other fields of surgery. The underlying emphasis has shifted from purely technical aspects to basic research and its clinical applications. Many of the techniques related to rhinoplasty and otoplasty have almost reached the stage of standardization, making basic or fundamental changes improbable. However, there have been technical modifications reported that aid in attaining the often elusive goal of the "perfect result."

RHINOPLASTIC SURGERY. The techniques of endonasal rhinoplasty devised by Jacques Joseph in the early part of the century, and which culminated in his monumental treatise "Nasenplastik und sonstige Gesichtsplastik" published in 1931[20], has proved its fundamental soundness for over one quarter of a century. Modifications and improvements of Joseph's principles have appeared, and are of real value particularly in the management of the septum and alar cartilages.

The role of the septum in rhinoplasty was subject to debate in the decade 1945 to 1955. The difficulty arose because of a lack of definition, namely, between the septal operation performed as an entity in contradistinction to its being performed as a combined operation with a rhinoplasty. Septal resection without a rhinoplasty found many advocates for radical removal of the septum at the turn of the century. These views were propounded by such authorities as Killian[22], St. Clair Thomson[33], and Freer[14]. In 1937, Peer[26] expressed the opinion that radical removal may be necessary for certain types of deflection but emphasized the need for a section of cartilage

in the anterior position to replace the septum for nasal support. Foman *et al.* in 1946[11], 1948[12], and 1951[13] described a similar method but incorporated the rhinoplastic approach of Joseph. This was endorsed by other authors of Foman's group, such as Cottle[9] and Ersner[10]. The adherents to this method did not clearly define the limitations of this procedure *vis-a-vis* rhinoplasty, although this was adumbrated. These techniques apply primarily to the correction of the deviated-dislocated septum alone and are rarely indicated when combined with a rhinoplasty except in the badly traumatized nose.

A more complex problem arises when correction of both an external and septal deformity are combined. The radical removal of the septum performed with an extensive rhinoplasty will often result in a depressed nose, because of lack of septal support. The exception is the severely traumatized nose. In these cases the dorsum is depressed and it is impossible to shift the septum without sacrifice of large sections of cartilage. It is then that a radical removal of the septum is indicated, but a dorsal implant of a bone or cartilage graft is necessary to correct the depression

To correct safely a deviated-dislocated septum associated with a rhinoplastic correction in the developmental type of deformity, the techniques advocating the shifting of the septal cartilage with minimal removal of septum were again emphasized. These were essentially modifications of the Metzenbaum[24] procedure, but incorporated rhinoplastic approaches. Modifications were presented by Safian[27], Salinger[28], Peer[26], Cohen[5], Seltzer[30], Steffenson[32], and Maliniac[23]. In 1950, a summary of the prevailing techniques was presented by the author before the American Academy of Ophthalmology and Otolaryngology (Becker[2]). A classification of the septal deformities and methods of handling them, and new approaches which materially improve the procedure were also presented. The article emphasized the basic principles of relocation of the septum with minimal sacrifice of cartilage.

In the *developmental* type of septum deformity, the cartilaginous septum is dislocated and deflected, and there is similar deviation of the underlying bony septum. The cartilage is separated from the bone by a smooth layer of perichondrium and periosteum. Because of this smooth sliding surface between them, the freeing of the cartilage at its junction with the underlying bone may be insufficient to prevent the septum from slipping back into the original position of dislocation. Moreover, the gradual pull of the shortened mucosa on the side of the dislocation may gradually shift the cartilage on its smooth bed back to its dislocated position.

To prevent such recurrence, the cartilage should not be cut at its junction with the vomer and maxillary bone but should be shifted as one unit with the bony septum. This is accomplished by completely fracturing the maxillary spine and crest and the lower end of the vomer from the floor of the nose, and shifting the entire lower end of the septum to the midline. Complete fracture through the bone prevents recurrence of the deformity, because the bone, unlike resilient cartilage, has no tendency to move after it has been fractured and set in position. Equally important is the fact that the fracture along the floor leaves the smooth sliding perichondral-periosteal surface undisturbed.

To ensure further the replacement of the septum in the midline and to prevent possible scar contracture or pull due to shortening of the mucosa, which results from shifting of the bone and

cartilage to the midline, an incision is made in the mucous membrane along the floor of the nose and lateral to the region of the fracture line. A free graft of mucous membrane or, better, a composite graft of mucosa and cartilage is placed over the raw area. The graft "takes" rapidly, and by the sixth or seventh postoperative day the nasal floor is completely healed. Tissue for grafting may be obtained from the shortening of the upper lateral cartilages and used as two grafts, or, if the septum is shortened, the removed section of cartilage with attached cutaneous-mucosal surface on one side may be utilized as an alternative composite graft along the floor of the nose. If tissue is not available from either of these sources, a mucosal graft from the undersurface of the inferior turbinate of the untreated nostril or a graft of buccal mucosa may be used.

After fracture through the bony septum, the septal cartilage should be cut vertically through its height, and, when necessary, narrow sections should be removed at the bends in the cartilage. The vertical incisions are carried down into the bone to join the fracture at the base. This should be accomplished without disturbing the perichondrium and mucosa on the opposite side. The perichondral attachments of the opposite side are left intact, not so much to ensure the viability of the cartilage, but to help prevent the anterior segment of cartilage from slipping back or down after it is cut. The perichondral and mucosal attachment thus acts as an adherent plate to the cartilage. The mucosal attachment on the opposite side of the anterior dislocation is disturbed only when it is desirable to thin down thickened cartilage or a ridge, usually along the floor in the region of bone and cartilage approximation. The deflected posterior portion of the septum may be removed according to the indications.

A problem Metzenbaum did not discuss is whether the upper lateral cartilages, which often are an integral part of the septal deformity, should be freed from the septum. When the cartilages are twisted along with the septum, a readjustment may be necessary to avoid pulling by the shortened upper lateral cartilage, which may cause recurrence of the deformity and prevent complete straightening of the twisted dorsum. This may be accomplished by detaching the cartilages from the septum, but this is not advisable because the upper lateral cartilages are intimately bound to the septum and function as lateral stabilizing extensions of the septum. These cartilages together with the septal cartilage thereby maintain the stability and form of the cartilaginous dorsum. In many cases, depending on the pathologic condition of the septum and the extent of the rhinoplasty, it is not necessary to free the upper lateral cartilages since shifting of the septum will readjust their position. In other cases, infracture of the nasal and maxillary bones plus shifting of the septum will readjust the position of the upper lateral cartilages. In still others, partial division of the upper lateral cartilages from the septum will take care of the matter. If complete division of one or both cartilages from their dorsal attachment to the septum is necessary, the underlying mucosa and perichondrium should be left intact and attached to the septum to maintain some fixation or continuity between upper lateral and septal cartilages. After the nose has been packed and splinted, fibrous adhesions will form a fixation between the cartilages.

Since it is highly advisable not to detach the upper lateral cartilages from the septum, a lateral freeing procedure can be used to mobilize them. This consists of freeing the lateral borders of the upper lateral cartilages

from the soft tissue and the maxillary bone, but not from the undersurface of the nasal bone, so that the central septal attachment remains. This will prevent the septal cartilage from slipping backward after it is cut vertically, even if the septum is resected behind the thoroughly freed and crosscut anterior segment of septal cartilage.

Sutures to approximate the septum to the columella are inserted without tension. The cartilage of the septum should not be sewn into a pocket between the two medial crura, for the natural contour of the membranous septum and columella may be destroyed resulting in an unnatural firmness of the nasal tip. Pink baseplate wax strips and small light vaseline packs are inserted into each nostril for hemostasis and to retain the position of the mucosal graft, the septal mucosa, and the skin lining of the lower lateral cartilages (which are trimmed during the rhinoplasty). Excessive packing, wiring of the septum to a tooth or piriform crest, and large wax plugs are unnecessary since the septum is completely mobilized and placed in a central position without any tendency for recurrence of the dislocation. The packing is left in position for 5 days, along with a dental mold and copper or tin splint for the external nasal correction.

THE TRAUMATIC TYPE. The septal deformities encountered after trauma may be divided into 3 groups: (1) the lateral type, which usually results from a lateral fracture of the nose with displacement of the septum from the vomerian groove and maxillary crest; (2) the depressed type, following a crushing frontal fracture and resulting in a bizarre septal configuration of buckling, twisting, reduplication and fibrosis; and (3) the latero-frontal type which combines the first two types, but more often is an accentuation of the lateral type.

The lateral type of traumatic septal deformity is corrected by methods similar to those used in treating the developmental type of deformity. However, in this type the cartilage is shifted from the vomer and maxillary crest, in contradistinction to the complete shift of bony and cartilaginous septum found in the developmental deformity. It is, therefore, necessary not only to use the methods outlined for the developmental type of deformities but to replace the septal cartilage on the vomerian groove. After the maxillary crest and vomer are fractured, the cartilage is cut at its base; the vomerian groove is cleansed of scar and periosteal tissue, and the cartilage is replaced. This may necessitate freeing or cutting the mucosa on the opposite side of the septum. In other cases, the added resection of an angulated strip of cartilage and bone at the juncture of vomer and septal cartilage may be necessary.

The depressed type of traumatic septal deformity poses a problem different from those of developmental and lateral traumatic deformities. In most cases, it is impossible to shift the septum back into position by the foregoing procedures, and wide resection of the crushed septum is necessary.

Whenever a wide or thorough resection is required, the stability of the nasal dorsum is endangered. However, when complete resection is necessary, the stability of the dorsum usually is not a problem, since the nose is already depressed. The procedure resolves itself into refracture of the nasal bones, thorough resection of the septum, including the dislocated lower portion, and implantation of a graft to the nasal dorsum and to the (usually) retracted columella. When the nose is both twisted and depressed, the upper lateral cartilages should not be freed from their attachment to the sep-

tum, since refracture of the nasal bones and complete resection of the septum will usually shift their position to the midline. When complete straightening does not result from refracture, either central freeing with mucoperichondral attachments to the septum or lateral freeing of the upper lateral cartilages will adjust their position.

The laterofrontal type of traumatic deformity results in a marked twist of the lower end of the septum and nasal dorsum, but the dorsum is not especially depressed. In this type, it may be necessary to completely remove the lower end of the septum. The question of stability of the dorsum becomes important in such cases. Since the nasal dorsum is in a relatively good position, it is almost always necessary to leave the upper lateral cartilages attached to the septum in order to protect the projection of the nose. Resection of the dislocated anterior septum, bilateral osteotomy of the frontal processes of the maxilla and lateral freeing of the upper lateral cartilages will in most cases correct the deviation and dislocation of the septum and straighten the dorsum.

During correction of the septum, it is highly advisable to maintain the support of the dorsum by leaving a narrow strip of subdorsal cartilage attached to the undersurface of the upper lateral cartilages. This strip or beam should extend to the extreme lower border of the septum to prevent sagging of the dorsum, particularly in the area which is dependent on the septum for maintenance of the dorsal projection. This beam should be cut vertically if indicated, a section of cartilage removed at the posterior angle of deflection and the base fractured, to shift the septum to the midline. It is possible in some cases to remove the lower portion of this cartilaginous beam and still maintain the profile, but only when the upper lateral cartilages are long, extending to the tip of the septum, and when the lower lateral cartilages are well developed and either firmly bound to the upper lateral cartilages or large enough to override the central portion of the upper lateral cartilages. Usually these conditions are lacking; instead, an area of septum about 0.75 cm. long is devoid of upper lateral cartilages, and the fibrous union of lower to upper lateral cartilage in this region is often too weak to prevent a depression just superior to the tip of the nose. Furthermore, if unusually firm fibrous attachments and overlapping upper and lower cartilages hold the nose in position without any septal support, there is always the risk that some slight trauma to the nose may cause a depression at a later date. The upper lateral cartilages alone cannot withstand much trauma without the additional reserve support of the septum. However, a narrow beam of septal cartilage, extending beyond and under the upper lateral cartilages and continuous posteriorly with the ethmoid plate and vomer, will furnish adequate reserve support to resist trauma. A large section or smaller segments of cartilage used to replace the completely resected septum will not furnish the stability and support that this beam of cartilage provides. However, even when this beam is preserved, it is necessary to replace a section of cartilage just behind and into the columella, not to serve as a support but to prevent retraction of the columella.

Obviously, only a limited rhinoplasty can be combined with this type of septal correction. Many cases of this type, however, can be adequately corrected by the methods outlined under the lateral type of deformity, thereby allowing a more extensive rhinoplastic correction. This is especially true in a long nose deformity which requires

shortening of the lower end of the septum.

A similar view was also taken by Converse[6] in an excellent article published in 1950 and also in his discussion of Becker's[2] presentation. His view also maintained that the septum should be manipulated into position by vertically cutting and removing narrow sections of cartilage. It is only in the depressed type and in some cases of the laterofrontal type that large sections of septal cartilage must be sacrificed and portions replaced. Other authors, Goldman 1956[16], and Huffman and Lierle 1954[19], concurred with these views.

In 1958 Holmes[18] presented a discussion before the American Academy of Ophthalmology and Otolaryngology with emphasis on the traumatic type of septal deformity where, in selected cases, he was able to shift the septum and relocate it to the midline and thereby elevate the dorsum. When an overlapping septum is present, that is, the upper portion of the septal cartilage overrides the lower segment, the septum is dissected and the upper portion pried up into position. If these procedures do not aid in filling the supratip depression of the nose, the Kazanjian[21] procedure of rotating the upper half of the alar cartilage to the dorsum is utilized to fill the defect. This may be used as an adjunct to a dorsal implant of bone or cartilage.

TRANSPLANTS IN PLASTIC SURGERY. The choice of a transplant or implant for the correction of depressed facial deformities has been a controversial subject for over 60 years. There have been advocates for the use of implants of various substances such as paraffin, metals, ivory, and plastics (polyethelene and acrylics). Implants of preserved homogenous (human) bone cartilage, and preserved heterogenous (animal) bone and cartilage have also had its exponents. Gradually the consensus of informed opinion has concluded that organic or inorganic foreign bodies are either absorbed or extruded and that the only logical grafts are autogenous bone and cartilage. This subject was discussed in detail in a panel discussion before the 1954 meeting of the American Academy of Ophthalmology and Otolaryngology held in New York. The panel consisted of John M. Converse, Oscar J. Becker, and Lyndon Peer[7], who concluded that autogenous grafts of bone or cartilage are the substances of choice. Only in exigencies should preserved human cartilage be substituted until a method of preserving homogenous cartilage makes it a viable graft rather than a tolerated organic implant.

The use of the word graft in itself implies a substance which when transplanted will survive with vital cells and resume its biological function in the new position into which it is placed after having been disconnected from another area of the body. This, of course, does not apply to implants which are non-living materials, either organic or inorganic.

The choice between cartilage and bone as a grafting material depends on the area of the head and neck in which it is to be employed. A general rule to follow, when possible, is to place bone on bone and cartilage on cartilage. Cartilage has the advantage of remaining viable and maintaining its shape whether it is placed on bone, on cartilage, or in fatty tissue, in contradistinction to bone which must be placed in contact with bone.

There is no single ideal grafting material for the repair of depressed nasal deformities. The conflicting statements and diverging opinions regarding transplants in medical literature are admissions that the ideal graft has not been

found. When an ideal substance is found, opinions as to its efficacy and versatility will probably be unanimous. However, the problem is really not simple; there are many determining factors to be considered in choosing proper transplants, and a single substance may not be satisfactory for all. If autogenous bone and cartilage are considered as alternate grafts, cartilage may be the graft of choice in one situation while bone is preferable in another (Becker[3]).

The writer's opinion, based upon results of a survey of the literature, experimental evidence, and personal experiences, is that autogenous grafts are the best. In certain exigencies other materials may be used as an expedient. These may include homogenous and heterogenous bone and cartilage, either fresh or preserved, and also alloplastic materials. Of the latter, homogenous or preserved human cartilage is preferred above all others.

Some factors determining choice of a graft include the size and character of the defect, availability of material, the general condition of the patient, and nature and vascularity of the recipient site.

Basically, there are 5 conditions which the ideal graft or implant should fulfil:

1. A graft should be tolerated by and acceptable to the tissues, (that is, cause no foreign body reaction and no tendency to extrusion); it should not be easily infected or set up a reaction after slight trauma.
2. A graft should be cosmetically acceptable (the results should warrant the surgical interference), that is, no distortion or warping, and it should be possible to model the graft with fine precision.
3. A graft should resist absorption and should retain its shape indefinitely.
4. A graft should be obtainable in sufficient quantity without causing undue pain to the patient.
5. The graft should engender a firm union without abnormal mobility.

At present there is no one substance which fulfils all these requirements.

The properties of both autogenous bone and cartilage approach these ideal standards but do not fulfil them completely. These are by far the best materials available. These constitute true grafts, whereas all other substances might be termed "implants." A true graft remains viable in the new location, carrying on its normal metabolic processes. This implies that the tissue remains alive, although contour may be modified and the graft may be absorbed partially and replaced by new tissue. An implant may be either an organic or an inorganic substance. Implants are tolerated by tissues but are not living tissues. Alloplastic materials, such as acrylics, hydrocarbons, and other synthetic chemical compounds, may be designated "inorganic implants."

Organic implants include fresh homogenous bone, preserved homogenous bone and cartilage, and heterogenous preserved bone or cartilage. These organic substances when implanted may remain for years as tolerated organic foreign bodies surrounded by dense fibrous tissue. This is especially true for preserved human cartilage. However, homogenous bone (fresh or preserved) is an exception and may be replaced by the host with new bone formed through either an inductive or a substitution process. This is most often observed where the bony implant is surrounded by bone, but this process does not always apply in a nasal (onlay) graft where there may be little contact between the bony surfaces.

Preserved human cartilage (also designated "isograft") may be valuable as an implant, but its fate is unpredictable

regardless of methods of preservation. It has been my experience that 35% of isografts are absorbed within 2 years, and this necessitates a secondary operation. Another 25% are partially absorbed but may retain enough structure to be clinically acceptable without need for further operative procedures.

A review of more than 200 cases in which preserved cartilage implants were used by me showed that fairly large implants subjected to relatively little tension or pressure have persisted for 2 or more years. A large implant may be encapsulated by fibrous tissue. This prevents absorption and aids in retaining the initial shape. Part of an isograft may be replaced by bone and dense connective tissue, and still the result may be acceptable. However, if there is undue tension or strain on an isograft, if an isograft is thin, if portions of the implanted cartilage were calcified before preservation, and if the bed is scarred and poorly vascularized, thereby preventing formation of a firm fibrous capsule, there may be a gradual erosion or dissolution of cartilage matrix. Presently available methods of preserving cartilage do not appear to influence persistence. Freeze-dried cartilage may be superior to cartilage preserved in merthiolate-saline solution, but further research is needed regarding this point.

Cartilage is chiefly used for reconstructive procedures of the nose and of the external ear. When large sections of rib cartilage are implanted to correct a complete saddle nose, there may be a tendency for it to curl or warp, to slip from its position or to be mobile, if it is not properly shaped. Cartilage, because it is held in position by fibrous tissue, should always be placed on a smooth bed and made to fit snugly against its bed, thereby avoiding a tendency for it to slip from side to side or "rock." When shaping a cartilage graft, deep nicks or cuts should be avoided, since this stimulates an ingrowth of fibrous tissue which may split the cartilage completely in half. Complete stripping of the perichondrium and removal of the outer or cortical layer are necessary to avoid curling or warping. Preserved cartilage does not have a tendency to curl.

Cartilage makes an ideal filling material for many defects when it can be used in a grated or diced form. In this form it may be inserted into a defect with ease; thus excessive mobility of the graft is avoided. If autogenous grated cartilage is employed, there is no tendency for it to curl or warp.

Bone, especially cancellous bone, is an excellent grafting material because of its large endosteal surface which allows it to heal rapidly with firm union. However, bone must be placed in contact with bone (the contact does not necessarily have to be firm) and, if possible, with the undersurface (cambium layer) of the periosteum over it. Its bulkiness, the difficulty of shaping it with fine contours, and the possibility of absorption when placed over cartilage or soft tissue are its main disadvantages.

Another factor influencing the absorption of bone grafts is the misdirection of stress and strain on the graft. Bone will be gradually modified in structure according to the functional stresses it serves (Wolff's law)[34]. Lack of function leads to bone absorption and atrophy. A bone graft placed over the cartilaginous nasal dorsum may be subject to unusual pressure and tension without stress, and this disturbance of function often results in absorption of this portion of the graft.

The most suitable donor site for cancellous bone is the iliac crest. This region is readily exposed, provides suf-

ficient bone for almost any plastic procedure on the face, and causes little discomfort postoperatively. Bone may be used to repair frontal, nasal, malar, and mandibular defects; it may be used as a single graft for the nasal dorsum or as small chips or ground mash for building out depressions of either malar, frontal, or chin areas.

For building out the lower columellar portion of a saddle-type nasal deformity, a septal cartilage graft is preferred if available.

The cartilage graft must be placed in a deep bed hollowed out to allow the graft to fit firmly. Hollowing of the bed has in most instances necessitated deepening of the saddle deformity, but I believe this was justified because I have observed little, if any, absorption of the cartilage. Inadvertently, a larger graft, half or slightly more than half the thickness of the rib, was necessary for the correction. These grafts did not warp or dislocate from their beds. An explanation for warping of cartilage, in cases where the cartilage had been completely denuded of perichondrium, was reported by Salinger[29]. He found that "this phenomenon is due to the difference in density between the cortical and medullary portions. . . . When the implant is cut from the core of the full thickness through its long axis, the complication of curling is extremely rare." A similar observation was reported by Gibson and Davis[15]. If a full thickness or a one-half thickness rib is cut longitudinally or if a central core of the cartilage is removed and the outer cortical layer of the cartilage is discarded, the graft will not warp. Without warpage, autogenous cartilage grafts seem almost ideal. However, if the graft is shaved too thin at either end, some distortion may occur which necessitates creating a deeper defect than was originally present. The chance of the very end of the cartilage curling, the pain and discomfort associated with the removal of cartilage, and the occasional inability to obtain a firm union to the bed are reasons why cartilage is not an ideal graft. Improvements in technique may eventually overcome these factors.

I have employed autogenous bone grafts in more than a hundred cases. These were used largely to correct either depressed or saddle noses and, in a few instances, to correct depressed frontal and malar fractures and also deformities of the chin. Results obtained have been quite variable. In 10% the grafts have been completely absorbed, and in 10 to 15% there has been partial absorption. These were cancellous iliac grafts (as advocated by Mowlem[25]) with extensive endosteal surfaces. Such grafts have been applied to the dorsum of the nose after wide elevation of the periosteum. I consider that the absorption of grafts has been attributable largely to improper choice of bone graft for particular cases. Ideal patients for bone grafts are those with defects primarily confined to large bony areas and with small cartilaginous defects. There should be a good bony base, such as occurs in a depressed fracture, where the periosteum can be widely elevated and the nasal bones rasped to open the Haversian canaliculi for rapid revascularization of the graft. Good contact can then be made between the thicker upper portion of the graft and the underlying bone, thereby increasing chances for complete survival of the graft. Bone makes an excellent graft and, compared to cartilage, is superior in many respects, for example, in fixation and absence of warping.

Bone may be partially absorbed if stresses and strains on a graft gradually modify its shape. This process of molding may proceed over a long period, sometimes for one to two years.

The change may in some instances be sufficient to require further operation. This is especially true in cases where a graft is used to aid in projecting the nasal tip. The gradual movement of the nasal and facial muscles with intermittent pressure on the lower end of the graft will lead to partial absorption.

Alloplastic materials are not recommended at present because of frequent foreign-body reactions, infections, and extrusions. However, eventually a plastic material may be found which will be absolutely inert, light in weight and able to withstand trauma because of its resiliency. If such a substance should become available, and there is every indication that this may be possible, then resumption of the use of alloplastics may be desirable.

What does the future hold? In all likelihood, a method will be found for preserving cartilage in banks without destroying the chondrocytes or the matrix with its valuable mucoprotein substance. Because of a low metabolic rate and absence of blood supply, storing in plasma may keep chondrocytes alive. Furthermore, the ability to control antibody-antigen reactions will further increase applicability of this method. This development may be anticipated as knowledge of cellular theory, chemistry, and allergy is further advanced. Grafts of this type would eliminate a need for operations on the chest.

THE NASAL TIP. The management of the nasal tip is probably the most exacting procedure in rhinoplastic surgery. This is so because judgment is of paramount importance and outweighs the purely technical aspects of the operation. Outstanding contributions on the technical aspects have been made by Foman[12], Converse[8], Aufricht[1], Safian[27], Seltzer[31], Goldman[17], and others.

The author, in a presentation before the American Academy of Ophthalmology and Otolaryngology in 1955, presented his concept for the management of the tip based on artistic anatomical factors[4].

The shape of the nasal tip is basically formed by the alar cartilages. However, depending upon the thickness of the skin, the amount of subcutaneous fat, areolar tissue and the activity of the sebaceous glands, the configuration of the tip may vary considerably from the basic structure of the alar cartilage. Furthermore, the form of the nasal tip is dependent on its relative position to the immobile or fixed structures, which suspend and hold the tip in position by firm fibrous attachments. A long, short, elevated or depressed septum, long or short upper lateral cartilages, the shape of the nasal bone and maxillary processes, the spine of the maxilla, the direction and tension of the surrounding muscles and fibrous connective tissue are determining factors in the position and shape of the nasal tip.

We are frequently surprised to note what remarkable changes in shape and position are accomplished by simply freeing the tip from the surrounding tissues. A further change is also noted when the last remaining suspensory attachment of the tip is freed by dissection of the alar cartilage from the enveloping skin. The skin at the nasal tip is immobile because of its firm adherence to the cartilage by dense fibrous connective tissue. This firm union aids in suspending and positioning the tip; thus, to mobilize it properly, the alar cartilage is detached from the overlying and surrounding skin. Frequently this may be all that is required to change the shape and direction of the tip. This is usually accomplished toward the end of the rhinoplastic operation. In thus mobilizing the alar cartilages, muscle fibers are also detached.

The muscles involved are the nasalis (transverse and alar), the dilator nares, the depressor septi, and occasionally a few slips of the caput angulari of the quadratus labii superioris. To mobilize the tip completely in a very dependent or long nose, it may be necessary to do a wide blunt dissection of the skin down to the orbicularis oris and laterally to the nasolabial fold, thereby freeing portions of the quadratus muscle.

The muscles which surround and envelop the nose are part of the mimetic muscles of the face, which have no real fascial covering such as cover the skeletal muscles of the body. Instead, they are found below and in the panniculus adiposis or superficial fascia, and the fibers are inserted directly into the dermis and cutis of the skin. This arrangement of muscle fibers is a direct outgrowth of the highly complex development of speech, whereby small muscle fibers were needed superficially to allow multiple variations of facial movements. A thick fascial covering, such as is encountered in the nonmimetic muscles, would leave the face blank and expressionless.

The nasal tip is corrected as one of the final steps of the rhinoplasty. After the immobile upper portion of the nose is corrected and the fibrous tissues which suspend the tip have been cut, the tip will frequently assume a new shape and position because of the change in relation to the rest of the nose. Further changes will be noted after complete mobilization of the lower lateral cartilages from the overlying skin.

An incision is made along the rim of the ala, following the lower border of the medial and lateral crura of the lower lateral cartilage. The incision is made a little inside of the cartilaginous rim, thereby leaving a small cuff of skin along the ala. This serves a two-fold purpose; it allows a small overlap of skin to help hold the alar cartilage in position when it is replaced, and it also prevents any scar contractures at the nostril border, which may develop if the incision is made too close to the rim.

A curved Joseph scissors is inserted into the incision and spread over the alar cartilage, completely freeing the cartilage from the overlying skin. The undermining is rather extensive, thereby detaching the cartilage from its fibrous connections to the outer border of the upper lateral cartilage, from its attachment to the septum, and medially from the opposite alar cartilage.

The alar cartilages can now be pulled down and exposed almost in their entirety. The lateral crus is still attached on its lateral surface, and the medial crus at its inferior border. The cartilages are still attached to the intact underlying vestibular skin.

At this point, the nose is placed in the position we ultimately wish it to retain. If the septum is long or if a large nasal spine is present along the floor, it is corrected by removing a section of the projecting lower end of the septum or the spine of the maxilla, or both. With the nasal structures completely mobilized, we are in a better position to evaluate whatever changes should be made in the alar cartilages. Usually the upper third or half of the lateral crus is found to be heavy, giving the nose a bulbous appearance. Direct markings are made on the skin to determine what amount of cartilage should be removed. Some narrowing at the angle of the lateral and medial crura is also indicated, along with the need for projecting or lowering the tip.

The alar cartilage is delivered and exposed to view, the dome (junction of the medial and lateral crura) is located and an incision made through the cartilage but not through the ves-

tibular skin. The cartilage of the lateral crus is then dissected from the vestibular skin for a few millimeters. This maneuver will narrow and project the tip without the removal of cartilage from the angle. The upper portion of the lateral crus is now incised and the bulbous portion removed, leaving the skin lining intact. If the overlying skin is thick and the nasalis transversus muscle is prominent, a small section of the underlying skin, muscle and fibrous connective tissue is removed with the cartilage. This will allow more shrinkage in the area and will permit a firmer adherence between the alar and upper lateral cartilages to develop because of the resultant raw area apposition.

After the alar cartilages are replaced in position there is usually an overlapping of the medial crus by the lateral crus. If the tip projects too much, the excess of the lateral crus may be trimmed. However, it is advantageous in most cases to leave this projection because it gives the tip a slight elevation above the dorsum, which is esthetically desirable.

The septum is again inspected to see if any further shortening is needed to help in elevating the tip. By waiting until this stage of the operation, the danger of overshortening the septum is avoided. The upper laterals are also inspected at this time; if any excess is present, it is also removed. It is surprising how little excess upper lateral cartilage is present. I find that if enough of the upper portion of the alar cartilage is removed, very little of the upper lateral need be sacrificed. This results in a better appearance, aids in preventing scar formation, and protects the function of the internal nasal aperture.

To close the septal-columellar incision, a few catgut or loosely tied black silk sutures are inserted to approximate the septal mucosa to the skin of the columella. The sutures have no real effect in elevating the nose; the nose should be in the desired position without tension on the sutures.

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DERMATOLOGY AND SYPHILOLOGY

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DRUG ERUPTIONS: A REVIEW OF SOME OF THE RECENT LITERATURE

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IN 1949, the problem of drug eruptions was reviewed in this Journal[9a]. Since then, there have been so many new drugs and such a wealth of material dealing with cutaneous reactions, that a re-appraisal of this subject is in order. Therefore, some of the current concepts of drug eruptions, as well as some of the recent types of drugs and their untoward cutaneous manifestations will be discussed.

We consider a drug eruption as: "a cutaneous, or oral mucosal process incident to the administration of drugs, or their split products, which come in contact with the affected part by way of the general circulation. These eruptions may result from medicaments administered by ingestion, injection, inhalation, or inunction. Absorption may occur from the skin, urinary bladder, conjunctiva, deep open wounds, vaginal, anal, oral and nasal mucosa, the pulmonary system, mother's milk, and transplacentally. In this concept, local application of medicaments producing eczematous contact eruptions are excluded"[9a].

There are often predisposing or contributory factors to drug eruptions. These include: other allergic processes; functional states, menses, menopause, pregnancy; organic disease; the presence of pigmentation or its absence; blood groups; nutritional states; and physical factors such as sunlight, heat, cold, and other vagaries of weather[129]. Hereditary[128b] and biochemical genetic factors, as well as cellular enzyme systems, may also play a role[116].

While the overall incidence of drug eruptions is relatively low as compared

with the total of all other dermatoses, there is evidence that this incidence is showing progressive increase[10,32,38,168]. Moreover, the importance of these eruptions exceeds their statistical occurrence since (a) they may resemble other cutaneous diseases, thus posing a problem in differential diagnosis; and (b) they may have rather disastrous, even fatal sequelae, proportionately greater than their relative incidence.

A clearer idea of the extent of the problem may be obtained by realizing that for the past few years an average of more than one new pharmaceutical prescription product per day has been introduced. Thus, in the past decade, this has amounted to approximately 4,000 new pharmaceutical products and 10,000 since 1938[88]. As Fisher[60] has pointed out, in a recent year some 400 new pharmaceuticals were produced, of which some 51 were new chemical entities *not previously known*. This does not include the host of proprietary medications. It has been estimated that over 350,000 substances have been employed as drugs of which about a thousand are in common use today.

According to Brown[23] approximately 500 of our current drugs may act as sensitizing substances. Others[1,108,151] have indicated that almost no current drug is exempt from the possibility of producing skin eruptions, and that almost all drugs, under appropriate circumstances may produce a variety of drug reactions.

Nearly everyone is exposed to drugs. Taken in the broad sense this includes vitamins, hormones, serums, vehicles, adjuvants, chemical substances used in diagnostic procedures, flavoring agents, dyes and coloring materials, disinfectants, preservatives, and antibiotics which may be found in foods (for example, penicillin in milk) and which are capable of producing drug eruptions[60]. Also, there may be cross-sensitization with non-drug chemicals which are immunologically and chemically related to drugs.

Several other reasons for the increasing incidence of drug eruptions are: (a) in some cases use of the same drug both systemically and locally enhances sensitization; (b) the use of drugs intermittently favors sensitization by reexposure; and (c) more and more drugs, which are often quite potent, are being used for relatively minor ailments[10].

It is important to note that cutaneous drug reactions are not monosymptomatic. They are often associated with related changes in other organs, such as: *Central nervous system:* "drug fever" or a central hypothalamic derangement; psychoneuroses or psychoses. *Hematopoietic System:* Blood dyscrasias; leukopenia, even to agranulocytosis, aplastic anemia; thrombocytopenia. *Liver:* toxic hepatitis, bile "inspissation" type, usually benign; or occasionally with parenchymal damage which may be extremely severe. *Kidney:* Albuminuria, crystalluria; occasionally anuria due to tubule blockage; acute interstitial nephritis and lower nephron nephrosis. *Respiratory tract:* laryngeal edema; bronchial mucus plugs, and "drug asthma;" Loeffler's syndrome, and the pulmonary changes (alveolar rupture) in anaphylactic shock. *Gastrointestinal tract:* Diarrhea; hemorrhage, gastritis, enterocolitis; other gastric and colonic disorders; moniliasis. *Mucous Membranes:* Stomatitis, gingivitis, gingival hypertrophy; conjunctivitis; vaginitis. *Vascular System:* Vasospasm; shock (? histamine release); periarteritis nodosa; thrombophlebitis; nodular vasculitis; serum sickness, which produces a variety of manifestations in divers tissues, including giant urticaria, angioneurotic edema, fever, and arthritis.

Drug eruptions may present them-

selves on the skin in a variety of clinical patterns[127a,132a]. Often they will mimic common dermatoses in their appearance. A partial list of such eruptions produced by drugs includes: acneiform; furunculoid; erysipelas-like; eczematous (with erythema, papulation, vesiculation, fissuring, weeping, crusting, and scaling); erythema multiforme-like; erythema nodosum-like; and "fixed" eruptions (that is, fixed, circumscribed, erythematous, edematous or bullous, and polychromatic pigmented eruptions); lichenoid and lichen planus-like; pemphigoid, ulcerating and vegetating; purpuric; bullous; scaling; purely erythematous or scarlatiniform and morbilliform; dermatitis exfoliativa; urticaria and angioneurotic edema[165]. Psoriasiform and hyperkeratotic lesions, granulomatous lesions, pruritus, hyperpigmentation (melanoderma), lupus erythematosus-like pictures[128a], have also been reported. Other cutaneous manifestations observed after treatment with certain medicaments are: alopecia, anhidrosis, cutaneous atrophy, glossitis, photosensitivity, stomatitis, seborrheic dermatitis-like eruptions; linea striae, hirsutism.

Lists of characteristic clinical eruptions, as well as their most frequently causal drugs may be found in a number of publications[1,10,128a,128b,168]. It should be emphasized that non-drug dermatoses have a tendency to predispose patients to reactions to certain drugs, or exacerbation of the existing eruptions. Those who have acne, acneiform eruptions and furuncles are more susceptible to iodides, bromides, androgens, and other steroid hormones. Persons suffering with atopic dermatitis are more susceptible to salicylates. Individuals with dermatitis herpetiformis are more susceptible to iodides, bromides, and thyroid substances. Patients with hypertrichosis are more susceptible to androgenic substances. Those with moniliasis and monilids are more susceptible to iodides and bromides. Persons with purpuric and hemorrhagic conditions are more susceptible to barbiturates, arsenicals, gold salts, sulfonamides, and salicylates. People who have recurrent herpes simplex are more susceptible to iodides, bromides, and salicylates. Individuals who have seborrheic conditions, intertrigo, infected and impetiginized eczematoid eruptions are more susceptible to gold salts, penicillin and anti-syphilitic arsenicals, and sulfonamides. And those who have urticarial eruptions are more susceptible to salicylates, iodides, bromides and a variety of other drugs[167].

PATHOGENESIS AND MECHANISM OF DRUG ERUPTIONS. The way in which drugs produce eruptions is still unknown. Many mechanisms have been proposed by a number of authors[1,10,23,32,128b,142,143a,b,144,168]. Based largely on Rostenberg and Webster's study[142,144] these may be outlined as follows:

1. *Pharmacologic-Toxic mechanism.* Implying an effect that would develop in anyone who took the drug in adequate dosage for a sufficient length of time: such as argyria after the prolonged use of silver salts, or gangrene after large doses of ergot. In other words, toxicity with cutaneous symptoms when drugs are used in larger doses or for more prolonged periods than normally permissible. There may also be secondary effects or side effects of the drug which are a part of its normal pharmacologic action, but may not be the primary reason for which the drug is employed, for example, somnolence or drowsiness as a side reaction with the use of antihistaminics.

2. *Enzymic interference or competitive phenomenon.* Many drugs have been found to alter enzymatic activity or compete for components in enzyme

systems. They may have selective toxicity for some enzyme involved in the intermediary metabolism of the affected cell. This includes gold, arsenic, and other heavy metal "poisoning" of given cellular enzyme systems.

3. *Photosensitization.* This implies the ability of certain agents to induce an alteration in the capacity of the skin to react to certain forms of actinic radiation. An inflammatory response to exposure to light on the skin may be induced by sulfonamides, porphyrins, some tranquilizers (mainly phenothiazine and chlorpromazine derivatives), and certain plants and oils.

4. *Intolerance or idiosyncrasy.* This is a purely individual phenomenon related to a person's inability to handle even small amounts of a drug; that is, doses which may be normal for the general population may, in relatively small amounts, cause abnormal response in certain individuals. This is *not* on the basis of hypersensitivity, but is probably on the basis of an inherent susceptibility or predisposition[50].

5. *Shwartzman phenomenon.* This may be responsible for certain hemorrhagic and necrotic cutaneous reactions. The Shwartzman phenomenon is a two-stage process in which the initial step consists of preparing the skin locally with a Shwartzman preparatory filtrate (usually bacterial products), and the second stage (following an incubation period of 12 to 24 hours) consists of eliciting a reaction in the already prepared tissue, usually via intravenous injection. It has been shown that a wide variety of bacterial substances are capable of acting as skin preparatory factors. The Shwartzman phenomenon apparently depends on the development of local hypersensitivity, yet it is not truly on the basis of an allergic mechanism. This is supported by the fact that the incubation period is only 12 to 24 hours, not long enough for the development of true (allergic) antibodies; also, the sensitizing agent ("skin preparatory factor") and the eliciting agent need not necessarily be the same, or even immunologically related. It is conceivable, therefore, that a patient may be given some medication to which he may be sensitive by virtue of previous exposure. If he has a "prepared" cutaneous site due to bacterial infection or other similar process, a reaction may then ensue which could provoke hemorrhage and necrosis at that site[144].

6. *Jarisch-Herxheimer reaction.* The Jarisch-Herxheimer effect is seen when a drug causes exacerbation of existing lesions or development of new ones, either because it too vigorously destroys the organisms for which it was used, or because it has such a wide bacterial spectrum that it kills many organisms besides the one for which it was administered. In either case bacterial products are released which may be toxic or irritant, or to which the host may be allergically sensitive. Some of the dyshidrosiform eruptions seen after the use of penicillin ("penicillids") may fall into this category[144]. It has been noticed often, upon the readministration of penicillin, patients do not manifest this type of eruption. It has been asserted that they have become desensitized. Rostenberg and Webster[144] hold that this is an erroneous interpretation, and that an allergic sensitivity to the penicillin probably did not previously exist. They believe that the eruption developed in the first place either because the penicillin destroyed enough organisms to release bacterial products to which the host was allergically sensitive, thus producing the reaction, or that the released materials were toxic enough to cause a reaction. In either case, the reaction did *not* arise because of an *allergic sensitivity to penicillin.*

The failure to manifest the reaction on re-administration of the penicillin would be explained on the basis that the same flora no longer existed, or was quantitatively so reduced that, where the penicillin was again given, the same bacterial products either could not be released or only in inadequate amount.

7. *Ecologic Imbalance.* Ecology is the study of the individual organism in relation to the total environment; this includes inter-species competition. The term ecologic imbalance refers to the disturbance of the normal inter-relationship of microorganisms[60]. The concept of ecologic imbalance is now used to explain certain reactions seen after antibiotic therapy. Antibiotics may create this chaotic state by destroying certain organisms, thus making conditions more propitious for the growth of others. As Rostenberg and Webster[144] have pointed out, there is a greater incidence of moniliasis in patients who have received antibiotics, especially broad spectrum antibiotics. This is not a complication to be taken lightly, as such cases can be fatal. The antibiotics destroy harmless, non-pathogenic bacteria as well as drug-sensitive pathogenic micro-organisms. Some of these non-pathogenic bacteria are necessary for the good health of the host, since they inhibit "overgrowth" of monilia. When these "restraining" bacteria are destroyed by the antibiotics, moniliasis may result[60], including such manifestations as perleche, stomatitis and proctitis. This concept, however, has been challenged[92]. In addition many organisms can be found living essentially as saprophytes, but under conditions of unrestricted multiplication, they may assume pathogenic qualities[144]; also the state of ecologic imbalance may cause overgrowth of resistant staphylococcus, proteus and pseudomonas bacteria, by suppression of competing organisms. This may result in virulent infections or super-infections with antibiotic resistant organisms, which recently have been of grave concern in many hospitals. It has also been noted that aside from the direct effect, of permitting overgrowth of certain microorganisms, the destruction of intestinal bacteria responsible for the synthesis of vitamin B factors may lead to hypo-vitaminosis, particularly riboflavin deficiency. Such deficiency may result in changes of mucous membranes and the skin: cheilitis and sore mouth and tongue may be found after administration of antibiotics; and it has been noted that vitamin B factors given simultaneously with antibiotics appear to minimize development of such lesions, as well as the frequently accompanying diarrhea[60]. Another possibility may be a change in pH as the result of the alteration of gastrointestinal flora. Fisher[60] has pointed out that not only is vitamin B metabolism interfered with by antibiotic therapy, but there may also be disturbance in vitamin K synthesis, leading to certain types of purpuric eruption. Melanoglossia (black tongue) following penicillin therapy may be due to nicotinic acid deficiency.

8. *Biotropic Mechanism*[144]. It has been postulated that bacteriocidal drugs may have a dual effect, necrotropic and biotropic. The necrotropic effect is the lethal action of a drug on certain microorganisms. The biotropic effect implies that this same drug may be stimulating to other microorganisms. While most so-called biotropic effects are probably on the basis of an ecologic interference (see previous section) some may be due to direct stimulation of the microorganisms themselves. It has also been held that allergic or sensitizing factors may play a role in this reaction, but in an indirect way. Thus, erythema nodosum seen

after the ingestion of sulfathiazole may not necessarily be an expression of a developing sensitization to the sulfonamide, but rather an indication of sensitization to a latent microorganism that the drug has stimulated into activity.

9. *Allergic Mechanisms*[30b,144]. Allergy is probably the basis of most lesions found in drug eruptions. Allergy may be defined as a specifically acquired alteration in the capacity of the individual to react, mediated by antibody formation. This implies that antigen introduced into the body gets to the site of globulin synthesis and causes enzymatic adaptation in the system concerned with the synthesis of globulin. As the result of this adaptation, the globulin produced has certain changes (chemical or structural) which show an ability to react with the originally introduced antigen. There are two major forms of manifestations of allergic sensitization in human beings[106]. These are: the immediate or urticarial type in which angioneurotic edema and even anaphylactoid reactions may occur (for example, seen after acute penicillin sensitivity). In these cases serum antibodies are often demonstrable, and desensitization is possible. However, many drug allergies are of the delayed or tuberculin-type reaction classically manifested in the skin (such as the eczematous exfoliative dermatitis of arsphenamine) in which antibodies cannot be readily demonstrated in the circulation by any of the usual techniques. Thus, there is no simple laboratory procedure by which the diagnosis can be made or the offending drug identified.

The characteristics of eruptions due to drug allergies and the reasons for believing that these eruptions are in general due to allergies have been outlined by Sulzberger[165]. The features of importance have not changed significantly since they were originally stated; however, it is of value to re-emphasize certain points. Eruptions may be produced by very minute amounts of a drug which may have previously been well-tolerated for years. Also, the eruption may occur long after the last medication, thus ruling out pharmacologic action and cumulative effect. In *most* persons, even after large dosage, eruptions do *not* occur; yet once such an eruption has occurred it is likely to recur upon subsequent minute exposures to the offending drug or to a related drug. In general, the clinical picture of the cutaneous response is entirely different from that produced by the pharmacologic or toxocologic action of the drug. Drugs with entirely different pharmacologic actions often produce identical eruptions; and the same drug is often capable of producing radically different manifestations in different individuals, or in the same individual at different times. Many drug eruptions occur only in certain predisposed individuals and, regardless of the deliberate increase in dosage, will not appear in the majority of individuals. As a general rule, drug eruptions can recur upon re-exposure to small amounts, even years after the last previous exposure and when the last demonstrable vestiges of the previously administered drug have been eliminated. The marked specificity of drug sensitivity can often be demonstrated. Individuals sensitive to one drug are frequently found to show no demonstrable sensitivity to isomers of that drug or to drugs with only slightly altered chemical constitution. But, just as has been demonstrated in sensitivity to living allergens, with drugs also, group specificity and cross reactions may be demonstrable. Many manifestations produced by allergy to living microorganisms or to natural allergens can be reproduced by drugs. They may exhibit incubation periods,

spontaneous flare-ups, and subsequent altered response to re-exposure. They can be ranged as to relative sensitizing capacity and tend to produce characteristic pictures. They elicit variations in host susceptibility, tend to select certain tissues and sites, are dependent upon environmental and dietary influences, may exhibit spontaneous fluctuations, and can produce changes which may persist for long periods.

10. *Fixed Drug Eruptions.* The term "fixed drug eruption" was introduced by Louis Brocq[22] to indicate an eruption in which the cutaneous manifestation appeared as round or oval apparently edematous plaques varying in size from that of a small coin to that of a palm, recurring on various parts of the body and accompanied by an itching or burning sensation. The patches were erythematous and dusky at their onset and had well-defined borders. At times the lesions progressed to form bullae. Desquamation or crusting after the bullous lesions appeared as the eruption faded, leaving pigmentation of variable shade and duration in the affected areas. A special feature of the eruption was its tendency to relapse with recurrence of the lesions in the same sites.

The first drug from which this phenomenon was noted was antipyrine. Many drugs are now known to be responsible for fixed eruptions. A list of such agents and a review of some of the literature on this subject was presented in a previous paper by Beerman[9a].

The mechanism of the production of fixed drug eruptions remains unknown. Although there has been some work done on this matter, the exact process has not yet been elucidated. The patient apparently becomes sensitized after exposure for a period of time during which there may be no ill-effects. Although specific antibodies can rarely be demonstrated, it is believed that an allergic hypersensitivity is the basis for the fixed drug eruption.

Some recent papers dealing with the subject of fixed drug eruptions are those of Cornbleet, Hoit, and Sickley[37]; Goncalves[71]; and Kennedy, Davis, Hennington, and Sternberg[86]. Stritzler and Kopf (**Stritzler, C.,** and **Kopf, A. W.:** J. Invest. Dermat., **34,** 319, 1960) reported the first example of fixed eruption caused by 8-Chlorotheophylline in Dramamine. The identical eruption occurred with 8-Bromotheophylline but none occurred to Theophylline or related xanthine derivatives. They observed a fixed drug eruption limited to the pigmented site produced by a 48-hour occlusive patch test with the suspected drug. They suggested that this constitutes a useful and harmless diagnostic procedure for determining the causative agent in fixed drug eruptions. If this procedure is effective in fixed drug eruptions of other causes, it will avoid the dangerous readministration test.

Specificity of drug reactions cannot be entirely demonstrated; and, while in general they are considered specific, there are enough variables in these findings to allow no generalizations on this subject. Sulzberger and Baer[167] state that in most drug reactions skin tests are generally of no practical value in the search for eliciting agents of drug reactions. Only in exceptional instances, such as in true eczematous and occasionally in true urticarial drug eruptions, will the appropriate skin test prove valuable. In most drug reactions no specific serologic changes or circulating antibodies can be discovered by available methods. In most drug reactions demonstration of the presence of a drug in the fluids or tissues of the patient does not constitute proof of the causal role of that drug. It proves only that the drug was encountered by

the patient. In most drug reactions failure to demonstrate a drug in the fluids or tissues of the patient does not exonerate the drug as a possible causal agent. It proves only that the drug is not present in demonstrable quantity or form at the time of the examination.

From the foregoing brief statement of principles of drug eruptions, it is obvious that the basic mechanism of this phenomenon is still little understood. As a guide for easy reference, we propose to list some of the newer drugs and some of the older drugs about which recently there has been interest in the literature. Since, as previously mentioned, the new drugs are legion[88], it is obvious that in this short survey only a few of these preparations can be mentioned and these only briefly.

Antibiotic Drugs. Penicillin. According to Feinberg and Feinberg[59], penicillin has become the primary problem in drug allergy. The cutaneous manifestations include urticaria, exfoliative dermatitis, contact dermatitis, erythema nodosum, and erythema multiforme. Purpura and periarteritis and serum sickness also have been reported. In addition to the strictly medical application of penicillin, reactions have been observed from this drug from hidden sources (Siegel, B. B., Bull. World Health Organ., **21**, 703, 1959) such as milk and foods[39, 175,180] and poliomyelitis vaccine[125,163,192].

It was contended that penicillin given to cattle for mastitis is capable of producing immediate and delayed generalized allergic reactions in persons highly sensitive to this antibiotic, and that the comparatively rare reactions attributable to this source have probably gone unreported or unrecognized. Zimmerman[191] observed penicillin urticaria (proved by penicillinase cures) from dairy products. However, the potentiality of ingested penicillin in milk to induce penicillin sensitivity in non-allergic individuals is suspected but not established. Although the Feinbergs[59], as well as Welch, Lewis, Weinstein, and Boeckman[182], have indicated the high incidence of penicillin reactions, especially cutaneous, the realization that this group of drugs was capable of producing so many reactions has not always been accepted as fact. Welch and his group reported that in a nationwide survey 901 of 1070 life-threatening reactions were due to penicillin and included severe reactions and angioneurotic edema. (1616 of 1925 milder reactions were due to penicillin and expressed themselves in urticaria and angioneurotic edema.) Johnston and Cazort[84a] have also discussed the potent and manifold effects of penicillin reactions. In 1951 Kitchen, Rein, Thomas, and Spoor[91] reviewed the literature for 1947 to 1950 and compared the number of people sensitive to penicillin to the amount used and found a decrease in reactions per trillion from 3.31 in 1947 to 0.84 in 1950. They attributed this to a decreased use of penicillin in oil and wax. They, too, found that urticaria was the most frequent reaction. This lowering of incidence, of course, is not borne out by the experience of many since the early years of penicillin therapy; and, perhaps, Kitchen and his co-workers' study represented a fond hope rather than a continued fact. On the other hand, The Philadelphia Academy of General Practice Penicillin Poll suggests that penicillin used judiciously is a remarkably safe drug[130]. The outstanding and, perhaps, most thoughtful survey of this problem was by Kern and Wimberley[90] in this Journal in which they pointed out the widespread and sometimes injudicious use of penicillin has resulted in an increasing number of allergic reactions, some of which

were quite severe, prolonged, incapacitating, and even fatal. They, as well as Anderson[3], have stated that penicillin ranks as one of the most common causes of allergic reactions to drugs. Individual studies of penicillin reactions of cutaneous types have been summarized in the review by Fromer[64b] and need not be further delineated in this shorter survey. However, Tuft and the Gregorys[170] have indicated that the most satisfactory skin test for the detection of penicillin allergy is the intracutaneous injection of 0.02 ml. of a concentration of penicillin of 10,000 units per ml.

The use of penicillinase in the treatment of penicillin reactions has been described by Becker and Bogle[8], and Minno and Davis[113]. But even this enzyme-drug is not without its dangers. Weiss and Crepea[178] and Reisch[135] have recorded cases of severe sensitivity to penicillinase following its use in penicillin reactions.

Goldblatt[70a] reported a severe reaction to griseofulvin. It consisted of swelling of the orbital, zygomatic, ear and lip areas; figured urticarial lesions over the entire trunk and extremities, with edema of the hands, wrists, feet, and ankles; and pain in the joints sufficient to produce almost complete limitation of motion. It is interesting to note that this patient had previously received penicillin in large doses for the treatment of an ear infection without incident. A single dose of 1 million units of procaine penicillin administered in December, 1958, resulted in some swelling of the arm around the site of injection; but a similar dose given in the hip the next day produced no untoward reaction. Quero (**Quero, R.:** J. Invest. Dermat., **34,** 283, 1960) also reported a case of urticarial and vascular allergic eruption following the ingestion of griseofulvin in a patient who was known to be allergic to penicillin. There was no evidence to indicate the existence of a common antigenicity in griseofulvin and penicillin, or immunologic cross-sensitivity to these two antibiotics.

Other Antibiotic Preparations. In addition to penicillin, other antibiotic preparations including the sulfonamides have been responsible, and still are, for a number of cutaneous reactions. This subject is covered in a general way in the papers of Nelson[119]; Huriez[83]; Lowell[99]; Rabut[133]; Crissey and Caccamise[41]; Welch, Lewis, Weinstein, and Boeckman[182].

Some of the reactions are difficult to to assess with respect to the causative drugs since so many antibiotics are now used in combination. However, a partial listing of some of the types of reactions reported will indicate their variety.

Pellagrous Dermatitis[114].

Erythema Multiforme[31].

Various Eruptions from Novobiocin[21,181].

Urticaria. Most noteworthy among the reactions have been urticaria, generalized erythema, or maculopapular eruptions; and serum sickness occasionally[132].

Photosensitization (Light Sensitivity Eruptions) due to Tetracycline Derivative (Declomycin) (Demethylchlortetracycline)[28a,58a,114a].

Tetracycline Provocation in Lupus Erythematosus[49].

Fixed Drug Eruptions from Aureomycin[183].

Jaundice from Novobiocin[40].

Pruritus Vulvae due to Aureomycin[11].

Black Hairy Tongue[169,186].

Dihydrostreptomycin, Aminosalicylic Acid, and Isoniazid Used in Therapy of Tuberculosis. Have caused reactions such as Loeffler's syndrome, as well as various pruritic lesions[42,58].

The fortunate aspect of some of these

potentially serious reactions is that recently the steroids have proven of value in treatment[27b].

Sulfonamides. The surprising number of eruptions still occurring from sulfonamide therapy is illustrated by sampling of recent reports of such.

Epidermolysis Bullosa[17].

Erythema Nodosum[9b,109].

Fixed Drug Eruptions from Sulfadiazine[67].

Other Drug Eruptions from Sulfadiazine[66].

Photo-Allergic Dermatitis due to Nadisan[25].

Various Cutaneous Reactions including Urticaria, Stevens-Johnson Syndrome, Erythema Multiforme, and Fatal Thrombocytopenic Purpura from Sulfamethoxypyridazine (Kynex)[5,13,65a,84,96,127,189].

Antihistaminics. Antihistaminics are a minor factor in causation of drug eruptions. The entire subject was discussed and documented by Barrock[7]. Patients exhibiting fixed drug eruptions, eczematoid dermatitis, and urticaria have been observed. All types of antihistaminics may cause reactions in sensitive individuals. For example, Tzanck and his associates reported 2 cases of phenergan dermatitis with photosensitization[171].

Antimalarials. The antimalarials constitute an important therapeutic means in the management of lupus erythematosus. Herrmann and his colleagues have studied the effects of mepracrine (atabrine) on the skin[75,112]. This problem was detailed in our earlier review[9a], but a number of interesting side-lights have recently appeared and may be of interest in individual case situations. Permanent anhidrosis, anhidrotic asthenia, and prolonged dermatitis have followed the development of atabrine dermatitis[150]. Young[190] observed a patient with melanosis due to Camoquin. Exfoliative dermatitis following administration of chloroquin has been reported[72]. Decrease in human hair color following chloroquin diphosphate was noted by Saunders and his coworkers[149]. Davis and Vander Ploeg[46] reported on 2 patients with acute porphyria, as well as other types of porphyria following chloroquine. Peterkin[128c] described a mepacrine eruption affecting a tooth. The process consisted of pigmentation of an incisor tooth. Simulation of jaundice by the action of quinacrine (atabrine) also has been seen[146]. Such difficulties in differential diagnosis which may arise when there are associated constitutional symptoms may lead to expensive hospitalization[146]. Quinine dermatitis in a patient who imbibed "gin and tonic" (quinine water) was reported by Novy and Lamb[120]. The cutaneous reactions, however, are not the most serious of those arising from the antimalarials, since aplastic anemia has been recorded on at least two occasions[45,121].

Quinine and quinidine have caused hematopoietic, as well as cutaneous problems, especially thrombocytopenic purpura[16,18,153,160]. In 1959, Bishop, Spencer, and Bethell[16] reported 6 cases of purpura due to this drug. The purpura was of the thrombocytopenic type. All 6 patients were women ranging in age from 38 to 69 years. Avoiding further administration of the drug and supportive measures, including blood transfusions, corticotropin, and corticosteroids, were beneficial.

Ataractic or Tranquilizing Drugs. The medical literature is replete with reports of the usefulness, and by the same token, reactions to the so-called tranquilizing drugs. This problem of cutaneous reactions is sufficiently large to merit a separate communication. It is only possible at this time to indicate the extent of the problem by listing a number of recent publications dealing with such phenomena. These are a

few of the general reviews on allergenicity of tranquilizing drugs[15,53,64b,79a,79c,118,161,162].

Some of the individual types of cutaneous reactions have been desquamation of the skin over the fingers[76]; contact dermatitis[95]; stomatitis and proctitis[20]; purpuric, maculopapular, vesicular, erythematosquamous eruptions[63,188]; photosensitization (photoallergy and photocross-sensitivity[26,27a,28,55,56,152,173]); hemorrhage from multiple sites associated with chlorpromazine-induced jaundice[61]; nonthrombocytopenic purpura[29]. In this connection agranulocytosis may be mentioned[93b] and jaundice[24,68,79b,98,107,174]. It is obvious from the reports that all the tranquilizers are capable of causing cutaneous reactions.

Antiepileptics. The newer antiepileptic drugs have been more productive of constitutional reactions rather than cutaneous ones. The well-known Dilantin hypertrophy of the gums and pigmentation from such drugs as Mesantoin[82] constitute the most common of the mucocutaneous manifestations. However, more recently visceral lupus erythematosus has been noted as a side effect of treatment with Hydantoin derivatives. Ruppli and Vossen[148] described 7 patients, aged 11 to 63, in whom, after use of Hydantoin derivatives, visceral lupus erythematosus developed. Three had full-blown symptoms including exanthema. All responded to discontinuation of the drug.

Halogens. Halogens still constitute an important source of cutaneous reaction because of their widespread use, especially the iodides, in radiography. In addition, a certain number of patients with acne vulgaris may have their acne aggravated by the ingestion of certain vitamins with minerals, including some iodine preparations.

Jones, Pariser, and Murray[85] discussed the subject of recurrent iododerma consisting of an unusual ulcerative and carbuncular cutaneous reaction on two separate occasions. The source of the iodine was finally traced to a preparation known as Quadrinal which contains, in addition to the iodide, ephedrine hydrochloride, theophylline calcium salicylate, and phenobarbital. Post[131] also reported on drug induced iododerma.

The subject of radiopaque source of iodide idiosyncrasy is fully discussed by Fromer[64b].

Ripka and Schwank[139] reported bromine acne after prolonged administration of pentamethonium. The eruption may have occurred because of poor renal filtration leading to bromine retention.

Urticarial reaction as a response to fluoride was described in 6 cases by Waldbott[177].

Heavy Metal and Arsenical Dermatoses. With the passing of the organic arsenicals in the treatment of syphilis, the problem of arsenical cutaneous reactions is limited largely to the result of use of the inorganic arsenicals. In spite of this, however, an occasional patient may develop organic arsenical reaction from such things as vaginal suppositories containing acetarsol[124]. The sources of the arsenic are many, and among them are asthma remedies[122] and other medicinal sources[6,155], and the metallurgical industry[6,80,157].

While there is still some argument about the ability of arsenic to produce cutaneous cancer, considerable literature has arisen in this regard[6,48a,80,122,157]. Snegireff and Lombard[157] have gone into the question of whether arsenic is actually the cause of so-called arsenical cancer; and on the basis of evidence examined in their survey, they concluded that the handling of arsenic trioxide, in the industries studied, did not produce a significant change in the cancer mortality of the plant em-

ployees. Hence, other factors, in addition to arsenic, must be considered of significance in the causal relation to cancer. Likewise, Frost and Spruth[65] conclude that "millions of pounds of arsenicals have been used in feeds in the last few years. As now used the arsenicals do not appear in any way to represent a hazard to human health." However, Hess[77] observed bronchial carcinomas in 8 vineyard workers in the course of 6 years. These workers had been using, before 1940, pesticides containing arsenic for dusting and spraying. Their bronchial carcinomas proved particularly malignant.

In addition to the cutaneous lesions and carcinoma, toxic hepatitis or cirrhosis has been reported on several occasions as being due to Fowler's solution[62,176]. This experience of hepatitis is not unique. Many of us have seen several such patients in private and clinic practice.

Among the miscellaneous reports of cutaneous reactions to heavy metals is a study of the bismuth blue line by Robinson[140]. Acrodynia following ingestion of mercury ointment[156] and successful treatment of dermatitis due to chrysotherapy with adrenocorticotropic hormone also have been observed[159].

Steroid Therapy. Although steroids are notably useful in the treatment of drug eruptions, they are not of themselves completely free of cutaneous ill effects. Kern's report[89] on the use and abuse of steroid therapy, notably in allergic disorders is a worthy guide for the employment of these drugs and an index of their potential noxious sequelae.

In 1950, Behrman and Goodman[12] were among the first to report on the cutaneous complications in patients treated with ACTH. They observed hyperpigmentation, acneiform eruptions, hirsutism, moon-face, striae atrophicae, delayed wound healing, and flattening of keloidal scars.

Bonner and Homburger[19] reported toxic dermatitis associated with Prednisone therapy.

Denko and Schroeder[47] reported ecchymotic skin lesions in patients receiving Prednisone.

Sullivan and Zeligman[164] made a careful and detailed report of the clinical and histologic differentiation between acne vulgaris and corticotropin acneiform eruption. The chief histologic difference is the normal appearance of the sebaceous glands in the corticotropin eruption as contrasted with the hyperplasia in acne vulgaris. The dual origin of acne vulgaris, namely adrenal cortex plus the ratio of androgens or progesterone, or both, to estrogens, contrasted with the single origin of the acneiform eruption, namely adrenal cortex, may account for the distinguishing gross and microscopic features.

DRUG ERUPTIONS AND L.E. PHENOMENON. For some time the L.E. phenomenon has been considered by some to be rather nonspecific and can be found in a number of processes other than lupus erythematosus, for example, in multiple myeloma, leukemia, hemolytic anemia, pernicious anemia, dermatitis herpetiformis, generalized moniliasis, and other cutaneous processes including sensitivity to certain drugs, penicillin, derivatives of hydantoin, sulfonamides, and, especially, Apresoline.

Miescher and Delacrétaz[110] examined 3 cases of penicillin sensitization, one with erythroderma, and a hydantoin-caused scarlatiniform exanthem, as well as several other systemic drug reactions, and found L.E. cells only in the patient with erythroderma due to penicillin reaction and in the patient with the hydantoin scarlatiniform rash. Since 1953, a number of instances of acute systemic lupus erythematosus-like

or rheumatic and febrile syndromes from hydralazine hydrochloride (Apresoline) have been reported[51,101,115,117,126,134]. In 1955, Henn, Parkin, Hargraves, and Odel[74] summarized the information up to that time on the subject and added an example of their own. Prior to their report, there were 9 instances in the literature describing a variety of delayed toxic reactions which developed in hypertensive patients who were taking hydralazine hydrochloride, in 6 of whom the L.E. cell phenomenon had been noted.

Ericson, Hines, Pease, and Brunsting[57] in 1956 reported a rheumatoid and lupus erythematosus-like syndrome as complications of Apresoline (hydralazine). Comens and Schroeder[36] studied 236 L.E. preparations on 105 hypertensive patients, receiving various doses of hydralazine hydrochloride for 2 weeks to 4 years. Ninety-seven patients were considered asymptomatic and were not suspected of hydralazine disease, and 8 definitely exhibited these disorders. Of the 97 smears only 10 contained occasional or rare L.E. cells, but the numbers were insufficient to suggest a diagnosis of disseminated lupus erythematosus. They concluded that the typical L.E. cell may appear, though rarely, in the blood of asymptomatic patients receiving hydralazine. However, since submission of the manuscript, 4 of their 10 patients showed positive smears with clinical and laboratory evidence of hydralazine disease.

Reynolds and Caldwell[137] questioned whether the hydralazine syndrome was hypersensitivity or toxicity. Their paper, however, contained but one case of an individual who developed hydralazine syndrome different from previously reported cases in that a clinical picture resembling acute rheumatoid arthritis appeared in a patient who had received a comparatively small amount of the drug over a relatively short time.

Siguier and his colleagues[154] reported the first hydralazine-induced lupus erythematosus in the French literature.

ALLERGIC ANGIITIS. In recent years acute episodes of nonthrombocytopenic purpura, secondary to inflammation of the walls of small dermal blood vessels, have been given many names, among which Winkelmann[187] feels that purpura rheumatica is adequate as a descriptive label. Many other names such as anaphylactoid purpura and allergic angiitis have been given to manifestations of this process. This disease has become such an important problem that it is necessary to realize that a patient may give a history of sensitivity to various medicines such as sulfonamides, antibiotics, barbiturates or anticonvulsants; or to chemicals such as insecticides; or the patient may develop his eruption following the injection of serum or other protein. This allergic angiitis or vasculitis has received considerable attention from Ruiter[147], McCombs and Patterson[104], McCombs, Patterson, and McMahon[105].

The cutaneous lesions are symmetrical indicating a hematogenous factor in the spread of the injurious agent. No matter whatever eruption is present some form of purpura will manifest itself eventually in the skin as a result of this reaction. Bullous lesions or even cutaneous infarction with ulceration may develop.

MISCELLANEOUS DRUGS PRODUCING REACTIONS. A number of medicaments are used by the laity and medical profession productive of eruptions of varying numbers, but do not necessarily fall into the previously discussed categories. A number of these will be mentioned briefly.

Antipyrine. Antipyrine was the first drug to have been demonstrated as responsible for fixed drug eruptions. Recently, Kennedy and his coworkers[86] studied the effects of this drug, found in certain patent medi-

cines. They found that of 9 patients who had had a previous reaction to the drug, the succeeding reaction was more severe and occurred more promptly than formerly. Bullous eruptions from antipyrine are more common in the Negro than in the white person. Patch tests yielded only one positive reaction, and that was in a patient in whom the results were positive only over the sites of the fixed drug eruption.

Oral Antidiabetic Preparations. An oral antidiabetic preparation, Carbutamide, has been found to produce eruptions. This is a sulfonamide derivative having the property of reducing the blood sugar level[54,138]. Carbutamide has yielded its place to Tolbutamid, known as Orinase, which is considered a safer preparation but still yielding 1.1% dermatologic reactions[43]. Further discussion of the reactions to oral agents in the therapy of diabetes may be found in the proceedings of the Conference on Current Trends in research and clinical management of diabetes[44]. Chlorpropamide (Diabinese), another of the oral hypoglycemic agents, has been reported as the causal agent of an erythema multiforme-like skin eruption by Rothfeld *et al.*[145].

Bromsulphalein. Bromsulphalein was responsible for a generalized severe coalescing morbilliform eruption, according to Deutsch, Neubuerger, and Jensen[48].

Butazolidin or Phenylbutazone. Mauer[103] reviewed the subject of toxic effect of Butazolidin, including mucocutaneous reactions. There were 12 reports of reactions in which the major disturbances were confined to the skin and mucous membrane. In addition, he reported the twenty-third death following the use of this drug which resembles aminopyrine in chemical structure. His patient had, also, exfoliative dermatitis.

Chloral Hydrate. Christianson and Perry[35] reported allergic cutaneous reactions in 7 patients as a result of chloral hydrate. Although they considered the reactions infrequent, they may, however, be severe. The literture reveals that various types of eruptions have followed the use of chloral hydrate. The commonest type are erythema, exanthemata, urticaria, and eczematoid dermatitis. Other types which have been reported also include hemorrhagic lesions, erythema multiforme, fixed eruptions, ulcerative lesions, pyoderma-like, and miscellaneous types.

Colchicine Derivatives. Alopecia totalis was noted after diacetylmethylcolchicine therapy of acute gout by Mikkelsen and his group[111]. Similar effects on the hair had been noted previously in treatment of leukemia disorders with this preparation. Malkinson and Lynfield[100] also have reported on colchicine alopecia.

Weiss and Segaloff[179] noted a transient depilatory reaction and other untoward effects to this same preparation which also is known commercially as Colcemid. Hollander[78] also noted vesicular dermatitis of the hands and fingers in a patient who was taking colchicine for gout.

Diamox (Acetazolcamiade). Two patients treated for congestive heart failure with Diamox developed eruptions as a result of the drug. One developed erythema multiforme bullosum; and the other, a papular eruption[158]. In the first patient the eruption disappeared after the drug was discontinued and ACTH and hydrocortisone were given. In the second patient the eruption disappeared after the drug was discontinued, recurred with further Diamox therapy, and then disappeared spontaneously, although the drug was continued. Other examples of Diamox

cutaneous lesions have been recorded (thrombocytopenia)[136,172].

Diuril (Chlorothiazide and Hydrochlorothiazide). Rogin[141] reported 3 women receiving Diuril who developed erythematous, papular and papulovesicular pruritic lesions on the upper and lower extremities, associated with edema of the hands and feet. Gesink and Bradford[69] encountered thrombocytopenic purpura following hydrochlorothiazide therapy. Harber, Lashinsky, and Baer[73a] also reported 3 patients with photosensitive eruptions due to chlorothiazide and hydrochlorothiazide. Two of the eruptions were lichen planus-like, and the third was vesicular and erythematous. The action spectrum in photosensitization due to these drugs was shown to be in the wave length between 2,750 Angstrom units and 3,100 Angstrom units; that is, the sunburn part of the ultraviolet spectrum.

Fumagillin. Drug eruption due to Fumagillin has been recorded by Anderson and Fleck[4].

Paraaminosalicylic Acid. Korst[93a] reported severe reactions to paraaminosalicylic acid. One of the prominent reactions was cutaneous, primarily urticaria. Alt and Spengler[2] subsequently reported the case of a 42-year-old man, with pulmonary tuberculosis, receiving isonicotinic acid hydrazide and paraaminosalicylic acid 3 times a day, who developed in a month a pruritic macular eruption. A patch test with paraaminosalicylic acid was positive.

Paraaminosalicylic acid, as well as reactions to other antituberculous drugs (streptomycin and isoniazid) have been recorded by Bereston[14].

Phenindione. Pastor and Tetreault[123] reported on the cutaneous reactions, among other types of reactions, due to phenindione, an anticoagulant preparation. They noted that various types of eruptions, especially morbilliform, have been described. East and Beamish[52], as well as Brooks and Calleja[22a], also recorded severe sensitivity reactions to phenylindanedione.

Poliomyelitis Vaccine. As would be expected, cutaneous reactions from Salk poliomyelitis vaccine have appeared. Samples of them include those reported by Stroud, Brodell, Lascheid, and Potts[163]; Chervinsky[33]; Christensen[34]; and Lipman[97]. The incidence of cutaneous reactions to this preparation is small (for example, 56 allergic reactions [anaphylaxis, urticaria, skin rashes, miscellaneous] after 184,000,000 injections). They may be urticaria, erythema multiforme, and others. It is possible that the penicillin in the vaccine may play a prominent role in the production of the lesions[125,163,192].

Succinylcholine (Anectine). Succinylcholine (anectine) a muscle relaxant has not produced many reactions since its introduction in 1950. Kepes and Haimovici[87] observed a patient who had skin manifestations and shock due to histamine release.

Temaril. Goldberg and Diamond[70], as well as Williams[185] have noted cutaneous reactions after the new oral antipruritic, Temaril. Goldberg and Diamond[70] noted one patient out of 160 who developed urticarial lesions, and Williams[185] only one patient out of 90 who developed a nonspecific cutaneous eruption.

Tetraethylthiuram Disulfide (Antabuse). Lewis and Bremers[94] reported a fixed drug eruption from Antabuse.

Thiouracyl Derivatives. Wilburn[184] noted an example of hair loss and pigmentation due to thiouracyl derivatives. This phenomenon was a non-hyperthyroid side reaction.

Trihexyphenidyl. Holt[81] reported spider angiomas occurring during treatment with trihexyphenidyl, a preparation useful in the treatment of

tremors and muscle rigidity in Parkinson's disease. This phenomenon occurred in 2 patients.

Smallpox Vaccine (Vaccinia). Leahy [93c] has mentioned cutaneous eruptions that may be caused by hypersensitivity to vaccinial proteins. These may develop 9 to 12 days after vaccination and include roseola, vaccinia, erythema multiforme, and urticaria.

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SUMMARIO IN INTERLINGUA

(See page 494 for original article)

Chronic Pancreatitis, Chylo-Ascites, e Chylothorace Indolor: Reporto de un Caso

Es presentate un caso de chronic recidivante pancreatitis indolor, responsabile pro diabete mellite, pro steatorrhea probabile, pro ascites chylose, e pro chylothorace sinistre. Le ascites esseva causate per obstruction del radiculas de chylo in le mesenterio del intestino tenue e del cisterna de chylo resultante del processo fibrotic que esseva initiate per le pancreatitis. Le chylothorace esseva causate per le transferimento de liquido chylose ab le cavitate abdominal al cavitate pleural via le vasos lymphatic del diaphragma. Chronic pancreatitis recidivante es per consequente un condition que debe esser addite al lista del non-neoplastic causas de ascites chylose. Tal ascites es rar.

PHYSIOLOGY

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A Review of the Countercurrent Hypothesis as a Mechanism for Concentrating the Urine. ROBERT W. WINTERS, M.D. (Departments of Physiology and Biochemistry, University of Pennsylvania, School of Medicine, Philadelphia, Pa.). In 1951, Hargitay and Kuhn introduced a bold new theory to account for the ability of the mammalian kidney to produce urine more concentrated osmotically than the plasma from which it is derived. The theory invoked the principle of a countercurrent multiplier in the loop of Henle as a means whereby a high osmolality of the fluids of the renal medulla could be achieved. Concentration of the urine was then conceived to occur by an osmotically-conditioned movement of water from the initially isoösmotic tubular fluid as it passed through the collecting ducts.

A review of the evidence reveals impressive support for the idea that some form of a countercurrent multiplier system is indeed operative in the loops of Henle, the driving force for which is the active transport of sodium. On the basis of microcryoscopic studies of the antidiuretic kidney, Wirz, Hargitay and Kuhn concluded that there was a progressive increase in osmolality of the renal medulla from corticomedullary junction to tip of the papilla. Direct chemical analysis of the medulla revealed a progressive increase in the concentration of sodium and of chloride per unit of tissue water. Micropuncture studies showed that although the proximal fluid was isoösmotic, fluid obtained from the tips of the loops of Henle was quite hyperosmotic, but equal in osmolality to the blood obtained from tips of the *vasa recta* as well as to the tubular fluid obtained from adjacent collecting ducts. On the other hand, fluid obtained from the early distal convolution was consistantly hypoösmotic, but farther along the distal convolution, the fluid again became isoösmotic.

The countercurrent hypothesis has several attractive features: (1) it provides a mechanism for generating high osmolalities, while avoiding any large osmotic gradients across single cell membranes; (2) it provides an explanation for concentrating the urine without the postulation of active transport of water.

Active Transport in the Stomach. C. ADRIAN M. HOGBEN, M.D., PH.D. (Department of Physiology, School of Medicine, The George Washington University, Washington, D.C.). Three facets of HCl formation were considered: the role of the gastric epithelial potential, localization of Cl^- transport and the mystery of fine structure. Several observations suggest that the distinctive potential difference is not a crucial part of the machinery generating HCl. Unlike other vertebrates, the elasmobranchs secrete H^+ ion without developing a mucosal potential difference. Further, H^+ ion production can be dissociated from the potential difference by exposing the mucosa to acetazolamide or a "$SO_4^=$ — Ringer" solution.

Knowledge of intracellular specific

activity when one surface of the mucosa is exposed to Cl^{36} allows us to resolve Cl^- flux into exchanges across the two faces of the epithelium; one separating cell from lumen, the other separating cell from interstitial or nutrient solution. Cl^- exchange across the luminal face is 10 to 20 times greater than across the nutrient face. Dinitrophenol, which reversibly inhibits both active transport and "exchange diffusion" of Cl^-, reduces the lumenal exchange by a factor of 30 and has little effect on the nutrient exchange, indicating that the carrier molecule is located in the cell membrane facing the lumen.

Weak anionic electrolytes are transported across the secreting mucosa from the luminal to nutrient solution. This can be ascribed to a preferential permeability to the unionized form. Because the net movement persists even when the luminal solution is made more alkaline than the nutrient solution, there appears to be a "microclimate" within the mucosa which is partially sequestered from the bulk solutions. Until we better understand the fine structure responsible for the "microclimate" we cannot reject the very attractive hypothesis that H^+ and Cl^- are transported by a forced exchange of Cl^- against HCO_3^-.

(Continued from page 432)

un recipeva initialmente le mentionate dosage plus 75 mg del droga al tempore del allectar se, durante que un secunde recipeva iste quantitate additional le octave die del experimento. Le duration medie del administration de hydrochlorothiazida esseva 13,5 dies (con limites mini- e maximal de 5 e 40 dies). Le evalutation del responsa diuretic esseva basate super alterationes del peso corporee e del excretion urinari de natrium. In le patientes con congestive disfallimento cardiac le responsa a hydrochlorothiazida esseva: excellente in 5, bon in 4, satisfacente in 2. Quatro del cirrhoticos e etiam le patiente nephrotic non responseva satisfactorimente al uso initial de hydrochlorothiazida. Per consequente, altere diureticos esseva addite in le effortio de tractar iste patientes adequatemente. Le uso concomitante de hydrochlorothiazida e prednisona resultava in satisfacente responsas in 3 del 5 casos. Le remanente 2 se monstrava refractori a altere formas de therapia, incluse combinationes de hydrochlorothiazida e merallurida o de merallurida con "cargation de chloruro" e alternante administrationes diurne de hydrochlorothiazida e acetazolamida. Le duo patientes cirrhotic con ascites es presentate como casos de documentation con graphicos monstrante le responsas urinari e le alterationes del electrolytos seral sub le conditiones del varie modalitates essayate. Nostre resultatos suggere le recommendabilitate de reservar le combinate therapia steroido-diuretic al patientes qui non responde al formas conventional de tractamento. Del altere latere, viste le methodo de investigation usate—*i.e.* le uso de un periodo initial de stabilisation de un duration de tres dies—le resultatos obtenite con hydrochlorothiazida in patientes con congestive disfallimento cardiac es ben comparabile con le resultatos reportate per altere autores con respecto al efficacia de iste nove agente diuretic.

BOOK REVIEWS AND NOTICES

MECHANISMS OF HYPERTENSION. By HENRY ALFRED SCHROEDER, M.D., Associate Professor of Medicine and Director, Hypertension Division, Department of Internal Medicine, Washington University School of Medicine. Pp. 379; 39 ills. Springfield, Ill.: Charles C Thomas, 1957. Price, $9.00.

THIS monograph is a major contribution to the literature on a subject of the first importance. Its great value rests in the first place on the fact that its author has devoted a life time of fruitful study and research in this field. There are chapters on The Complex of Factors in Human Disease, Basic or Constitutional Factors in Hypertension, Neurogenic Factors Affecting Mechanism, Nephrogenic Factors Affecting Mechanism, Factors Influencing the Conversion of Neurogenic to Nephrogenic Hypertension, Trace Metals and Cardiovascular Disease, Some Mechanisms in Atherosclerosis, Practical Methods for Modern Therapy of Hypertension and a Preliminary Approach to the Treatment of Atherosclerosis. The material is presented in a very clear and orderly fashion with numerous illustrative case reports and brief pithy comments, particularly the short "Summary" paragraph at the end of each chapter. There is appended a bibliography of 448 references carefully selected from a vast literature (between 1920 and 1950 there were over 16,000 references in the literature on hypertension). The book is highly recommended to all physicians.

R.K.

FIEBER UNSPEZIFISCHE ABWEHRVORGÄNGE UNSPEZIFISCHE THERAPIE. By PROF. DR. FERDINAND HOFF. Pp. 145; 36 ills. Stuttgart: Georg Thieme Verlag, 1957 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $3.85.

THIS little volume is an important contribution in a field that, since the introduction of antibiotics, has been in eclipse. Nevertheless, the nonspecific mechansims of defense, the curative power of fever and the capability of the body to overcome disease by its own powers continue to be pertinent to certain problems in the therapy of infections. Recent discoveries, such as the preparation of pyrogenic lipopolysaccharides which can produce fever by doses of a fraction of a gamma, and the discovery of properdin which provides a scientific explanation for a nonspecific destruction of bacteria, have renewed the interest in such therapy. The author, who has been a student of the subject for over 30 years, here presents a scholarly review and evaluation of old and new material. Among the 14 chapters are such topics as: Fever Therapy and Nonspecific Protective Processes; The Role of the Nervous System (in these processes); The Role of the Pituitary-Adrenal System (here is an excellent discussion of the adaptation syndrome of Selye, which points out its shortcomings and places it in a more logical perspective); The Role of Other Humoral Agents, Antigens, Leukopoietins and Pyrogens; The Role of the Leukocytes; Destruction of Bacteria and the Properdin System; Fibrinolysis, Alteration and Ferment Activities; The Relation to Local Inflammation; Nonspecific Resistance, Pro-munity and Immunity; Nonspecific Therapy in Medical Practice. This book deserves careful study by all students of immunology and therapy of infections.

R.K.

MANUALE DI SEMEIOTICA MEDICA, VOL. 1. By F. LENZI AND A. CANIGGIA. Pp. 593; 296 ills. Torino: Edizioni Minerva Medica, 1957. Price, L. 7000.

THIS volume represents a new approach in the teaching of medical symptomatology to medical students. History taking and physical diagnosis come early in the medical curriculum when the student is as yet ignorant about the symptoms of disease which his history must elicit, and to the signs which he should recognize in his examination of the patient. This book in its first section, "History," gives a concise but adequate statement of certain basic items in human experience and bodily functions in health and their alterations in disease. The next section deals with the objective general examination describing average normal findings and their pathological modifications: including, for example, the facies, decubitus, psyche and sensorium, general body build, sexual characteristics, state of nutrition and hydration; the examination of the skin, with consideration of cyanosis and pigmentation, icterus, edema and inflammation; the temperature and respiration; the lymph-glandular system. The

last section discusses the blood and the several methods of examination of blood and blood components. There are nearly 300 illustrations, many in color. This volume is designated No. 1. There is no indication of the number or contents of possible future volumes. The work is an excellent addition to teaching texts and is highly recommended to students who read Italian. R.K.

THE INCURABLE WOUND AND FURTHER NARATIVES OF MEDICAL DETECTION. BY BERTON ROUECHE. Pp. 177. Boston: Little, Brown and Co., 1957. Price, $3.50.

THE medical profession as well as the general public will welcome this new volume of medical detection stories. Mr. Roueche has proved his ability to spin exciting yarns in this field by his earlier volume, "Eleven Blue Men." Physicians will find the new group of stories instructive as well as entertaining. It was his recalling of the cause of the cyanosis of those eleven patients that enabled a young house officer in a Philadelphia hospital to diagnosis the illness of his patient who had eaten adulterated fish. R.K.

MANUAL OF THE INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES, INJURIES, AND CAUSES OF DEATH. 2 volumes (Vol. 1 and Vol. 2). 1955 revision. Pp. 393 and 540. Geneva: World Health Organization, 1957. Price, $6.75 for the two volumes.

THIS is the seventh revision of the Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death as adopted by the 9th World Health Assembly. In this edition consideration has been given to the use and feasibility of the International Classification of Diseases as a diagnostic index for hospital case histories, thereby extending its great usefulness. There are appended the regulations of the World Health Organization regarding nomenclature.

R.K.

SOUTH AFRICAN SNAKE VENOMS AND ANTIVENOMS. BY POUL AGERHOLM CHRISTENSEN, M.B.(COPENH.). Pp. 129; 43 ills. Johannesburg, South Africa: The South African Institute for Medical Research, 1957.

OF the nearly six hundred species of venomous snakes of the world, almost fifty occur in South Africa. The present volume is an excellent survey of the snake bite problems of southern Africa. What makes this volume of more general interest is the discussion of the effect of venom, in which the author has presented much original work in addition to gathering the significant publications from all parts of the world. The book is a valuable contribution to medical herpetology. R.K.

INDUSTRY AND TROPICAL HEALTH III. Proceedings of the Third Conference of the Industrial Council for Tropical Health, Harvard School of Public Health, April 16-18, 1957. Pp. 261; 20 ills. Boston: Harvard School of Public Health, 1957. Price, $10.00; professional rate ($5.00).

THE Third Industrial Tropical Health Conference was held in April, 1957, in Boston under the aegis of the Harvard School of Public Health. Like its predecessors, the Conference attracted many experts in Tropical Medicine from many parts of the world as well as research workers in the field of communicable diseases for an exchange of information and experiences in both theory and practice. The growing importance of these meetings is evident from the increasing number of participating industries. This volume is the record of the papers there presented and the discussions they effected, and affords much first-hand practical information. The Harvard School of Public Health is to be congratulated on the continuance of this valuable forum which its former Dean, James Stevens Simmons, had the vision to begin. R.K.

FARMACOLOGIA, MATERIA MEDICA Y TERAPEUTICA, VOLUME 2. BY LUIS E. CAMPONOVO AND ALFREDO J. BANDONI. Pp. 601; illustrated. Buenos Aires: Lopez & Etchegoyen, 1957.

AFTER an interval of nearly four years there now appears the second volume of this elementary text in pharmacology, materia medica and therapeutics. The material is arranged in four chapters dealing respectively with Antiseptics and Disinfectants (263 pages), Heavy Metals (82 pages), Chemotherapeutic Agents and Antibiotics (222 pages), and Immunology, including Vaccines and Sera (18 pages). Drugs are discussed under their names as these occur in the Argentine pharmacopoeia or the International pharmacopoeia, or both, and, in addition, there are given many of their proprietary trade names. The index covers both

volumes. The presentations are concise, clear and adequate for the use of students.

R.K.

ADVENTURES IN MEDICAL EDUCATION. By G. CANBY ROBINSON, M.D., LL.D., Sc.D. Pp. 338; 9 ills. Cambridge, Mass.: Harvard University Press for the Commonwealth Fund, 1957. Price, $5.00.

THIS book is the happy result of a rare combination of gifts, talents, and opportunities in its author: a physician, teacher and scientist whose professional life span covers the most active period of advance in medical education and medical science; one who early showed talent as an organizer and administrator and therefore was in demand throughout his career to exercise that talent; one who always took a very personal attitude in his work, whether toward colleagues, students or patients; one with a fine gift of writing. While it deals with his personal experiences, it is not primarily autobiographical, but rather a presentation of the development of institutions and programs in which he had active part. An adequate amount of background and historical material lends depth and continuity to the narrative. There is an opening chapter on the Growth of American Medical Education. The next tells the story of Johns Hopkins University School of Medicine which he attended from 1899 to 1903. "Hospital Days," from 1903 to 1910, were spent chiefly at the Pennsylvania Hospital in Philadelphia, as assistant pathologist in its Ayer Laboratory and as resident physician, with a brief stay as assistant to a surgeon at Clifton Springs Sanitarium, a year in Munich under Friedrich Müller and a year in practice and some teaching at Pennsylvania. When the Hospital of the Rockefeller Institute was founded, he became its first senior resident physician (1910-1913). In 1913 he was called as associate professor of medicine to the Washington University School of Medicine and as acting dean played a major part in the reorganization of its faculty and curriculum. Then from 1920 to 1928, as dean and professor of medicine, he directed the reorganization of Vanderbilt University School of Medicine. From 1928 to 1934 he was the first director of the New York Hospital-Cornell Medical College Association when those two institutions began their medical center development. Then came a year as visiting professor of Medicine at Peiping Union Medical College. From 1935 to 1941 he turned to a new and pioneering interest in the social aspects of medicine at Hopkins. In the latter year he became director of the National Red Cross Blood Donor Service that by 1945 had collected over 13 million pints of blood. In 1946 he became the executive secretary of the Maryland Tuberculosis Association, retiring at the end of 1955 to write this book. Its pages teem with interesting people and challenging problems. Everyone concerned in medical teaching and research should read it.

R.K.

DIE INFEKTIONSKRANKHEITEN DES MENSCHEN UND IHRE ERREGER. VOLUMES I AND II. Edited by PROF. DR. A. GRUMBACH, Zürich, and PROF. DR. W. KIKUTH, Düsseldorf. Pp. 1702; 56 ills Stuttgart: George Thieme Verlag, 1958 (Intercontinental Medical Book Corp., New York, U.S. Agents). Price, $47.15.

THIS book presents an extended coverage of the infectious diseases and the parasitic infestations of man. As its 1700 pages and two volumes attest, it is intended to be not only a mere textbook for the student but a reference work for the practitioner. The first 400 pages deal with general topics: The Beginnings, Development and Clearing of Infectious Diseases; Host-Parasite Relationships and Their Characteristics; The Causes of Infectious Diseases in Man: Bacteria, Rickettsia, Viruses, Fungi, Protozoa and Helminths; General Epidemiology; Active and Passive Immunization; Serum Sickness; Basic Concepts of Chemotherapy; Disinfection and Sterilization; De-Infestation; Nomenclature and Taxonomy. Then follow, in the Special Section, the presentations of the Bacterial Infections, Rickettsioses, Viral Infections, Fungus Infections, Protozoal Infestations and Worm Infestations. The book is the work of 17 contributors, 11 in Germany, 4 in Switzerland and one each in Sweden and the United States. The coverage is of a high degree of excellence and relatively complete. There are extensive bibliographies after each section. The most serious drawback is a lack of illustrations. The book should find a wide appeal.

R.K.

THE STORY BEHIND THE WORD. By HARRY WAIN, A.A., B.S.M., M.D., M.S P.H., Health Commissioner, Mansfield-Richland County, Ohio. Pp. 342. Springfield, Ill.: Charles C Thomas, 1958. Price, $8.50.

THIS book places the emphasis on the history of over 5,700 terms and names commonly used in the medical sciences. As a

result, one-fourth of the terms are eponyms or the names of medical personalities, many of them contemporary. Since this is not a medical dictionary, the author had to pick and choose, evidently avoiding simple terms whose meaning was clear or without historical significance. One wonders why some proprietary drug names were included. The book will be found interesting for browsing as well as reference. R.K.

ANIMAL DISEASE AND HUMAN HEALTH. By JAMES LIEBERMAN AND 69 OTHERS. Pp. 485; illustrated. New York: New York Academy of Sciences, 1958.

THIS book is eloquent testimony to the rapidly growing importance of animal reservoirs for human disease. It consists of 41 papers presented at a Conference on Animal Disease in Human Health by the New York Academy of Sciences in collaboration with the Communicable Disease Center of the United States Public Health Service. The papers are grouped under the following headings: The Viral Encephalitides, Other Problems in Virology (including the Orphan viruses and counterparts of human viral diseases in animals), The Leptospiroses, Recent Developments in the Epidemiology of Rabies, Ornithosis, Other Human Disease Problems (such as murine typhus, Q fever, brucellosis, parasites, salmonellosis, listerosis, tuberculosis, ring worm, Newcastle disease, cat scratch fever, sylvatic plague, and biological warfare), Selected Chronic Diseases (rheumatoid arthritis, pulmonary adenomatosis), International Programs. The volume performs a great service in collecting much valuable information in this rapidly growing field. R.K.

RELIGIOUS DOCTRINE AND MEDICAL PRACTICE. By RICHARD THOMAS BARTON, M.D., Associate Consultant, University of California, Los Angeles. Pp. 94. Springfield, Ill.: Charles C Thomas, 1958. Price, $3.75.

THIS little volume is a practical guide for the physician, the nurse, the dietitian and the medical administrator who are confronted by the religious beliefs and doctrinal habits of patients. In six well-written chapters there are discussed The History of the Religious Approach to Healing; then the doctrinal backgrounds and the beliefs of medical import as manifested by the Religions of Asiatic Origin, those of Middle Eastern Origin, those of Western Origin, those of American Origin and the Religions of Healthy-Mindedness. Each section is well documented by a supplementary reading list. The book is a valuable contribution that should be in the hands of every practicing physician and of ancillary medical personnel. R.K.

PUBLIC HEALTH LAWS OF PENNSYLVANIA. Edited by DAVID STAHL. Pp. 767. Pittsburgh: University of Pittsburgh School of Law, 1958.

THIS is a monumental contribution, the joint effort of the staff of the Law School and of the School of Public Health of the University of Pittsburgh carried out over a period of 8 years. During this same period the legislature of the State of Pennsylvania took cognizance of this study and implemented many of its recommendations of new and forward-looking legislation. The volume, therefore, represents an analysis, notation and codification of the Public Health Laws of Pennsylvania up to and including the legislative session of 1955-56 and with a supplement of the 1957 legislative session. There are chapters on Public Health Administration in Pennsylvania, Vital Statistics, Communicable Disease Control, Hospitals; Food, Meat, Milk, Beverages and Eating Places; Drugs and Alcohol, School Health, Child and Maternal Health, House Sanitation, Air Pollution, Industrial Health; Stream Pollution, Water, and Public Bathing Places. There is a complete index. This volume will be welcomed by all who are interested in the legislative aspects of public health administration. R.K.

VERDICT FOR THE DOCTOR: THE CASE OF BENJAMIN RUSH. By WINTHROP AND FRANCES NEILSON. Pp. 245; 14 ills. New York: Hastings House, 1958. Price, $4.50.

MOST everyone knows of the John Peter Zenger case of 1734 in New York which established the idea of freedom of the press in America. No less important, but far less known, is the suit brought by Dr. Benjamin Rush against William Cobbett resulting in the latter's conviction for libel. This book tells the story of that trial in 1799 in a most interesting manner. What is most important, it gives a fine survey of the conditions which led to the trial. These include, in the first place, the political background: Rush a signer of the Declaration of Independence was an ardent follower of Jefferson and a proponent of Democratic-Republican doctrine while Cobbett, a Briton, not only held with Hamilton and the Federalists, but was also

an avowed monarchist. Then there is a medical controversy of the day: for or against blood-letting, especially as applied to the great yellow fever epidemic of 1793 in Philadelphia and again in the outbreak of 1797, with Rush as the chief proponent of phlebotomy and mercurial purgation. The book presents a splendid analysis of the basic legal principles which were involved and of the arguments presented by counsel for both sides. It is highly recommended to all readers and especially to all physicians and students of medicine. R.K.

Safe Handling of Radioisotopes. International Atomic Energy Agency. Pp. 99. Vienna, Austria: International Atomic Energy Agency, 1958 (International Publications, Inc., New York, U.S. Agents). Price, $1.00.

This is a compendium of safety regulations issued by the International Atomic Energy Agency in Vienna, discussing in considerable detail the regulations which are recommended for safe handling of isotopes, such as already exist, and are required, in United States installations using isotopes under license by the United States Atomic Energy Commission. For the benefit of those who are setting up radioisotope laboratories, considerably more detail is found in these recommendations than one ordinarily finds and it is a convenient and compact collection of opinions from world authorities on such levels as recorded with the various instrumentations available. It is recommended to all radioactive isotope users. R.R.

The Work of WHO 1957. Official Records of the WHO No. 82. Pp. 183. Geneva: World Health Organization, 1958. Price, $1.25.

The annual report of the Director General of the World Health Organization marks another milestone in its ever-growing program of promoting health. The first section presents a general review with reports on such subjects as malaria, eradication of communicable disease, public health services, environmental sanitation, atomic energy and health and others. Part 2 presents a discussion by regions including Africa, The Americas, Southeast Asia, Europe, The Eastern Mediterranean and the Western Pacific. In Part 3, are discussed cooperative activities with other organizations. Part 4, which comprises three-fourths of the volume, lists the many projects with a brief description of the aims, assistance provided by WHO and the work done in each throughout the world. The material has been stated in somewhat briefer fashion because the volume has appeared at about the same time as a more complete publication entitled "The First Ten Years of the World Health Organization." R.K.

Annual Epidemiological and Vital Statistics. Pp. 699. Geneva: World Health Organization, 1958. Price, $12.00.

This is the eighth annual volume of vital and health statistics published by the World Health Organization. Each year this volume becomes larger and the number of subjects dealt with increases as the machinery for collecting and recording vital statistics in greater and greater detail is extended under World Health Organization guidance in all countries. All text and terminology are expressed both in French and English. This report now enables physicians and public health workers to form an idea of the multiple aspects of the health of the peoples in different parts of the world. R.K.

Insecticide Resistance in Arthropods. By A. W. A. Brown, Ph.D. Pp. 234; 29 ills. Geneva: World Health Organization, 1958. Price, $5.00.

The growing complexity as well as extent of insecticide resistance in arthropods are creating public health problems of increasing magnitude. This volume is, therefore, an important contribution. The first chapter deals with The Nature and Characterization of Resistance, with a review of data now available, and a discussion of Resistance as a Pre-Adaptive Phenomenon, The Physiological and Genetic Origins of Resistance, Its Development in Model Experiments and in Practice in the Field, Counter-measures involving the Continued Use of Insecticides, The Surveillance of Susceptibility and of Resistance, and Biological Factors in Susceptibility Levels. Chapter 2 presents the problems from the standpoint of groups of arthropods that are characteristically disease vectors for man, including body lice, several types of fleas, 32 species of mosquitoes and some flies. A long third chapter (81 pages) is devoted to all aspects of resistance in the house fly. The concluding chapter takes up the problem in groups characteristically not vectors of disease for man, including various

muscid flies, midges, fruit flies, bed bugs, roaches and certain ticks. There are 27 pages of references. R.K.

Remedies and Rackets. By James Cook. Pp. 252. New York: W. W. Norton & Co., Inc., 1958. Price, $3.75.

Twenty years ago the American Medical Association brought out some articles under the heading "Nostrums and Quackery." Mr. Cook brings the subject up-to-date. Chapter headings are self-explanatory and eloquent: Our Billion Dollar Medicine Show, The Chamber of Horrors, Tired Blood, Aspirin: Plain and Fancy, Teasing of Arthritics, Vitamins and Voodoo, Tonics and Salesmanship, Cold Cures, Reducing Pill Razzle Dazzle, The Imitation Tranquilizers, The Truth about Drug Prices, Adventures in the Skin Game, How to Grow Old Carelessly, The Triumph of Liver Pills, Cancer and Quackery, Nostrums in New York, One hundred and Seventy Million Guinea Pigs. The picture which he draws is a disquieting and unattractive one. Mail order quackery is today the most lucrative of all forms of criminal activity and from the standpoint of the criminal the safest. The chapter on Tired Blood should be required reading for all television viewers. Doctors would do well to recommend this book to their patients. They could learn much themselves, particularly from the chapter on The Truth about Drug Prices. R.K.

Men, Molds and History. By Félix Martí-Ibáñez, M.D. Pp. 114. New York: MD Publications, Inc., 1958. Price, $3.00.

This book consists of six lectures and four essays by Dr. Martí-Ibáñez. The lectures were delivered in five annual symposia (which he helped found) and one international symposium on Antibiotics. Their titles include: Historical Perspectives of Antibiotics, Philosophic Impact of Antibiotics on Clinical Medicine, The Next Half Century in Antibiotic Medicine, Antibiotics Today and the Medicine of the Future, Antibiotics and the Problem of Medical Communication; On Treating the Whole Patient; Words and Research. The four essays are on Quest of the Broad Spectrum, The Meaning of Greatness: Sir Alexander Fleming; The Art of Translation and the Science of Antibiotics. The central theme is the impact of antibiotics on medical practice, on medical thinking, and speculation as to future development. The author brings to his task a refreshing philosophic outlook, a vivid imagination and a facile pen. The reader will find this book to be interesting and stimulating reading, even if he is not in full agreement (for example, the need for a Professor of Antibiotic Medicine on every medical faculty). R.K.

Centaur: Essays on the History of Medical Ideas. By Félix Martí-Ibáñez M.D. Pp. 714. New York: MD Publications, Inc., 1958. Price, $6.00.

As he says in his Preface, literature, psychiatry and medical history have been the burning lights that lured his roaming spirit. Over the years he has written two novels, a number of short stories, about 2,000 cultural and journalistic articles and more than a thousand lectures. From all this, he has selected for this volume some of the articles and lectures of the last decade, dealing more or less directly with medical history. They are loosely grouped in sections entitled: Medical Humanities, Tapestry of History, Philosophy of Medicine, Medical Communication, The Mirror of Psychiatry, Through the Psychological Glass, The Artist's World and a chapter of Editorials. The book provides entertaining as well as instructive reading. R.K.

Clinical Epidemiology. By John R. Paul, M.D., Professor of Preventive Medicine, Yale University School of Medicine. Pp. 291; 37 ills. Chicago: University of Chicago Press, 1958. Price, $5.00.

As the author points out in his preface, this volume presents the application of a new philosophy to old diseases: the concept that epidemiology is concerned with all aspects of the ecology of disease, dealing with a wide range of circumstances under which people get sick. The first section of the book presents definitions and concepts in historical perspective. In Part 2, there are developed the principles of the newer concept of epidemiology, including clinical approaches, mortality rates, illness rates, charting of data, population information, host susceptibility, serological epidemiology, the environment. In Part 3, the practical applications of epidemiology are illustrated in connection with certain sample diseases including rheumatic fever, coronary occlusion, poliomyelitis, hepatitis, and arthropod-borne virus infections The author brings to his task a long, rich and fruitful experience in this field. The book is strongly recommended. R.K.

RADIATION BIOLOGY AND CANCER. University of Texas M.D. Anderson Hospital and Tumor Institute. Collection of Papers presented at the 12th Annual Symposium on Fundamental Cancer Research, 1958. Pp. 493; illustrated. Austin: University of Texas Press, 1959. Price, $8.50.

THIS is a report of the papers presented at the 12th Annual Symposium on Fundamental Cancer Research in 1958 at the M.D. Anderson Hospital in Houston, Texas. It is well presented by such authors as Furth discussing radiation neoplasia and the endocrine system, Howard-Flanders discussing the physical and chemical processes in radiobiology, Kaplan discussing radiation induced leukemia in animals, Maloney discussing the same with reference to man, and many others whom we have come to consider as authorities in the general subject of radiobiology and in cancer research. Included are comprehensive discussions on fundamental radiobiology, ultra violet induced neoplasia, induction of neoplasia by ionizing radiation, a discussion of mutagenic and carcinogenic, and of human genetics in radiation, and finally a discussion of medical applications of radiation by a group of clinicians with great experience in radiation therapy and in radiobiology. The book is strongly recommended to those interested in the fields of cancer, genetics, and radiobiology. R.R.

THE FIRST TEN YEARS OF THE WORLD HEALTH ORGANIZATION. Pp. 548; 28 pages of illustrations. Geneva: World Health Organization, 1958. Price, $5.00.

THIS book truly marks an important milestone in the history of the greatest organized health effort in the world's history. Part 1 tells of the International Sanitary Conferences that began in 1851, and the earlier health organizations, especially that of the League of Nations. Part 2 describes the establishment of the World Health Organization in 1948 as a development out of the San Francisco recommendations prefacing the United Nations Organization. Part 3, comprising the major part of the book, summarizes ten years of work in the manifold activities of the World Health Organization. Not only has this ten-year period been marked by many significant advances in public health but the new organization has had much more extensive responsibilities, aims and implementation than its predecessors. Therefore the stories set forth in the 23 chapters of the third section are a record of unparalleled achievement in such fields as malaria, tuberculosis, venereal diseases, treponematoses, virus diseases, zoonoses and veterinary public health, international quarantine, epidemiological and statistical services; atomic energy in relation to health, environmental sanitation, nutrition, mental health, maternal and child health, health education and training, pharmaceutical standards and nomenclature, health laboratory methods, public information and others. The annexes, which comprise the last 75 pages, include The Constitution of the World Health Organization. Its Members and Associate Members, and a record of various committees, conferences and organizational data. This book should command a wide range of interest. R.K.

PRINCIPLES OF RADIATION DOSIMETRY. By G. N. WHYTE, National Research Council, Ottawa, Canada. Pp. 124; 43 ills. New York: John Wiley & Sons, Inc., 1959. Price, $7.00.

THIS is a comprehensive treatment of the fundamental physical principles underlying methods of radiation dosimetry, discussed at highly technical level, and meant for the radiation physicist with a strong background in mathematics. The mathematical treatment, and the theoretical level of the book makes it at once highly desirable for the radiation physicist, and not satisfactory for the physician in radiation, who will find its treatment to be at a level somewhat higher than he wishes. R.R.

OCULAR ALLERGY. By FREDERICK H. THEODORE, M.D., AND ABRAHAM SCHLOSSMAN, M.D., with chapters by WILLIAM B. SHERMAN, M.D., AND ROBERT S. COLES, M.D. Pp. 420; 111 ills. and 2 color plates. Baltimore: The Williams & Wilkins Co., 1958. Price, $12.00.

THE relative ease of relating cause (exposure to allergen) to effect (local reaction) in ocular manifestations of allergy because of their superficial location and the finding of eosinophils in the conjunctival sac early established the allergic nature of the acute manifestations. This, in turn, plus the immunologic thinking of such ophthalmic pathfinders as Dr. Alan Woods, have resulted in the study and recognition of the less obvious ocular allergies, so that today the allergology of the eye is among the most complete. This volume is an excellent presentation of the subject. After an introductory chapter on The Basic Principles of Allergy by W. B. Sherman, there are considered the several

types of Allergy of the Conjunctiva, Allergic Dermato-Conjunctivitis, Drug Irritations of Conjunctiva, The Treatment of Allergic Conjunctivitis, Vernal Conjunctivitis, Diagnostic Aids in Conjunctivitis, Allergy of the Eyelids including Edema and Eczema with a discussion of the important contact allergens; Allergy of the Cornea, Interstitial Keratitis, Allergy of the Sclera, Allergy of the Uvea (by R. S. Coles); Allergy of the Lens, Allergy of the Retina and Optic Nerve. The 111 illustrations, some in color, are all excellent. The book is highly recommended. R.K.

DIFFERENTIALDIAGNOSE INNERER KRANKHEITEN. By PROF. DR. ROBERT HEGGLIN. 6th ed. Pp. 819; 517 ills., many in color. Stuttgart: George Thieme Verlag, 1959 (Intercontinental Medical Book Corp., New York, U.S. Agents). Price, $18.35.

THIS is the 6th German edition of a text that first appeared only 7 years ago and has been translated into Italian (3 editions) and Spanish. The excellence which this record bespeaks is not far to seek: clarity of presentation, balance, good judgment in selection of material, the author's philosophic approach and his wisdom in pointing out possible causes of error. After an opening chapter on General Viewpoints, Methods and Symptomatology, there are chapters that discuss the differential diagnosis of these presenting complaints: Anemia, Fever, Headache, Dyspnea, Disturbances of Cardiac Rhythm, Electrocardiographic Changes, Cyanosis, Chest Pain, Hypertension, Hypotension, Pulmonary Infiltrations, Hilar Enlargements, Lymph Adenopathy, Abdominal Pain, Diarrhea, Constipation, Jaundice, Splenomegaly; Hematuria, Albuminuria, Pyuria, Cylindruria; Edema, Pains in the Extremities and the Region of the Spine, Palsies of Voluntary Movements (a new chapter in this edition) and Loss of Consciousness. Format and print are pleasing. The illustrations, many of them in color, are excellent and numerous (517). The book is highly recommended to those who read German, Italian or Spanish. An English translation would be welcome. R.K.

NAVY SURGEON: AN AUTOBIOGRAPHY. By REAR ADMIRAL LAMONT PUGH, MC, USN (RET.). Pp. 459; 21 ills. Philadelphia: J. B. Lippincott Co., 1959. Price, $5.00.

THIS is the biography of a man who served as a Marine in World War I, then studied Medicine, entered the Medical Corps of the Navy and eventually rose to be its Surgeon General. His experiences covered a wide range of duty, ashore and afloat, and in World War II and the Korean War, the latter while he was Surgeon General. No "desk" officer, he was ever in touch with all phases of activity of his Corps and as Surgeon General he visited wherever a Naval Medical officer might be stationed. Born and raised on a Virginia farm, he tells of his boyhood, his Marine Corps service and his education in the first ten chapters, "The Green Years." Part 2, "Heyday," deals with his ever-widening horizons and activities as a Naval Surgeon and administrator up to and including his command of the Naval Medical School. In December, 1946, he became Deputy Surgeon General when only 49 years old, then Surgeon General in January, 1951, a post which he held until 1955. Then he continued as Commanding Officer of the National Naval Medical Center at Bethesda until a second coronary seizure forced his retirement in 1956. There were also many important contacts and responsibilities involving civilian medicine during this period. These "Vintage Years" are covered in Part 3. All whose privilege it has been to know him are impressed with his forcefulness of character, his high purpose, his ability as a Surgeon and administrator, and his enormous capacity for work, all well-seasoned with a genial personality, a delightful sense of humor and a genius for making friends. To these he adds a retentive memory, a goodly store of notes made along the way, a philosophic outlook and a light and happy style of writing that makes this book a joy to read. Ever forthright and outspoken in his conversation, he has continued to be no less frank in his writing. The book teems with judgments and opinions which he drops as freely as a collie dog sheds hair. One is reminded of the self-characterization of a certain radio personality: "Sometimes wrong, but never in doubt; opinionated, but loveable." This reviewer is grateful to Lamont Pugh for this fine book and recommends it highly to all readers, lay or medical, civilian or military, as instructive, challenging and entertaining reading. R.K.

V. A. PROSPECTUS RESEARCH IN AGING. Pp. 125; 48 ills. Washington: Veterans Administration, 1959. Price, $1.50.

AT a meeting of the Veterans Administration Advisory Committee for Problems of Aging, held in May, 1958, there were pre-

sented a group of papers that proved to be highly interesting and informative and that aroused much pertinent discussion.. They are here made available to a wide range of interested readers. The topics include Aging of Molecules, Aging of Cells, Aging of Organs, Aging of Individuals and Aging of Groups.

R.K.

CELLULAR AND HUMORAL ASPECTS OF THE HYPERTENSIVE STATES. Symposia of the Section on Microbiology, The New York Academy of Medicine, No. 9. Edited by H. SHERWOOD LAWRENCE, M.D. with 25 contributing authors. Pp. 667; 120 ills. New York: Paul B. Hoeber, Inc., 1959. Price, $18.00..

THIS is the ninth in a series of volumes recording Symposia held at the New York Academy of Medicine. The 18 chapters of the present volume are the work of 43 authorities in the cellular and humoral aspects of hypersensitivity. The subjects which are covered include: Biochemical Aspects of Reactions, Cytologic Events, Induction of Delayed Hypersensitivity, Hypersensitivity of Simple Chemicals, The Toxic Effects of the Antigen-Antibody Reaction, Models for Hypersensitivity States, The Transfer of Hypersensitivity, General and Local Vascular Reactions, The Immunology and Pathogenesis of Serum Sickness, Agammaglobulinemia, Endotoxins in Bacterial Allergy, Endotoxins of Gram-Negative Bacteria, Damage by Tissue-Adjuvant Emulsions, Hypersensitivity Disease and Others. There are numerous references to the literature and valuable informal discussions have been recorded. All workers in the field of hypersensitivity will wish to have this highly useful collation of material at their service.

R.K.

DANGEROUS MARINE ANIMALS. By BRUCE W. HALSTEAD, M.D., Director, World Life Research Institute. Pp. 146; 86 ills. and 1 color plate. Cambridge, Maryland: Cornell Maritime Press, 1959. Price, $4.00.

THIS little volume contains much interesting and practical information on a variety of dangerous marine animals. There are four chapters; the first is a brief summary of earlier knowledge in the field and of some significant publications. Chapter 2 deals with marine animals that bite, notably sharks, the manta, barracuda, the moray eel, the grouper, sea lion, the killer whale and tridacna clam. Chapter 3 discusses the marine animals that sting, notably the jelly fishes, certain mollusks, stinging worms and sea urchins, the sting rays, and a large number of fishes. The final chapter presents marine animals that are poisonous to eat, including various mollusks, sharks, rays, eels and fishes. There are brief presentations of medical aspects, including symptom pictures, treatment and prevention. The book is profusely and well illustrated. It should find a wide appeal.

R.K.

WILLIAM HARVEY'S DE MOTU LOCALI ANIMALIUM, 1627. Edited, translated and introduced by GWENETH WHITTERIDGE. Pp. 163; 1 ill. New York: Cambridge University Press, 1959. Price, $10.50.

IN his De Motu Cordis, William Harvey promised the publication of a future work on the local movement of animals. Until now it has existed only in the form of manuscript notes in the British Museum. Miss Whitteridge has performed a signal service in transcribing Harvey's obscure handwriting, in translating and annotating the material. The Latin appears on the left hand page, the English translation on the right. This is indeed a fitting way to celebrate the tercentenary of Harvey's death and will receive the approbation of all who are interested in medical history and particularly those interested in Harvey.

R.K.

MECHANISMS OF HYPERSENSITIVITY: HENRY FORD HOSPITAL INTERNATIONAL SYMPOSIUM. Edited by JOSEPH H. SHAFFER, M.D., Henry Ford Hospital, Detroit, GERALD A. LOGRIPPO, M.D., Henry Ford Hospital, and MERRILL W. CHASE, PH.D., Rockefeller Institute for Medical Research, New York. Pp. 754; illustrated. Boston: Little, Brown and Co., 1959. Price, $18.50.

THIS volume represents the proceedings of a Symposium on Mechanisms of Hypersensitivity held at the Ford Hospital. The 47 papers by 65 specialists, working in the several aspects of research and practice in the field of allergy, are grouped in 12 sections which bear the headings: Heterogeneity of Antibodies, Detection of Antibodies in Human Sera, Effects of Antibody and of Antigen-Antibody Complexes on Intact Cells and Whole Organisms, Permeability Factors, Complement in Allergic Responses, Autoantibodies, Delayed-Type Hypersensitivity Reactions, Immunologic Unresponsiveness, Tolerance and Rejection of Tissue, Hormones and Allergic Responses, The Role of Mycobacteria in Allergic Manifestations and Some Factors

Modifying the Response to Allergens. These titles give an indication of the thoroughness and detail with which this rapidly growing subject has been covered. There are numerous illustrations, chiefly photomicrographs. Significant discussions have been recorded, including discussions by designated participants and general discussion. Workers in the field will find this a valuable compilation of reference material. R.K.

CHOLERA. WHO Monograph Series, No. 43. By R. POLLITZER, M.D., George Williams Hooper Foundation, University of California, San Francisco. Pp. 1019; 23 ills. Geneva: World Health Organization, 1959. Price, $20.00.

CHOLERA was at one time a major health problem of every country in the world. Today it exists in certain endemic foci in Asia from which it occasionally erupts in epidemic form on that continent, killing tens of thousands every year. Its importance as a major health problem still continues: This volume, therefore, assumes great importance in the literature on the disease. Its eleven chapters discuss History, World Incidence, Bacteriology, Problems in Immunology, Bacteriophage, Pathology and Morbid Anatomy, Laboratory Diagnosis, Clinical Pathology, Diagnosis and Treatment, Epidemiology, Prevention and Control. Much of the material has grown out of previous reports and studies under the auspices of the World Health Organization which now publishes the work in its series of monographs. This volume constitutes a rich storehouse for reference. It is highly recommended. R.K.

The Cytopathology of Virus Infection (Ann. New York Acad. Sci., Vol. 81, Art. 1). By ROBERT LOVE AND 36 OTHERS. Pp. 214; illustrated. New York: New York Academy of Sciences, 1959. Price, $4.50.

THIS is a report of a conference held by the New York Academy of Sciences and is one of the most complete summaries of morphological changes effected by viruses in cellular systems. The monograph is extensively illustrated. M.K.

Formulaire Astier. Memento de Médecine Pratique. 11th ed. Pp. 1,772. Paris: Masson et Cie, 1960. Price, 50 NF.

A pocket-sized formulary and outline of treatment including emergencies which French physicians continue to find helpful, witness the 11th edition. R.K.

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